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Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial
A Paediatric Acute Respiratory Intervention Study (PARIS 2)

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Title Page

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Roles and Responsibilities:

Trial Registration:

This trial is registered in the Australian New Zealand Clinical Trial Registry

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Author contributions:

DF, AS, DS, SD and FB were responsible for identifying the research question and contributing the drafting of the protocol. All authors have contributed to the development of the protocol and study design. DF was responsible for drafting this manuscript, with comments and feedback from all other authors. KG provided expert statistical advice and input, BG developed the health economic measures and analysis. All authors attest to having approved the final manuscript. DF and AS take responsibility for the manuscript as a whole.

Competing interests:

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Steering Committee:

Each site is represented by at least one member for the steering group.

Data and Safety Monitoring Board (DSMB):

Phil Sargent, Scott Burgess, Kristen Gibbons (stat).

Ethics approval: The study protocol has been reviewed and approved by ethics committees in Australia (Children's Health Queensland Human Research Ethics Committee, HREC/15/QRCH/159 and Ethics Committee of The University of Queensland 2016001491) and New Zealand (Health and Disability Ethics Committee HDEC 17/NTA/135).

ABBREVIATION	TERM
AHRF	Acute Hypoxic Respiratory Failure
BiPAP	Bi-level Positive Airway Pressure
CEWT	Children's Early Warning Tool
CPAP	Continuous Positive Airway Pressure
CRF	Clinical Research Form
ED	Emergency Department
EWT	Early Warning Tool
Fi02	Fraction of Inspired Oxygen
FPH	Fisher & Paykel Healthcare
FRC	Functional Residual Capacity
ICU	Intensive Care Unit
LCCH	Lady Cilento Children's Hospital
MDI	Metered Dose Inhaler
MET	Medical Emergency Team
NGT	Nasogastric Tube
NHF	Nasal High Flow
NIV	Non-Invasive Ventilation
PCCRG	Paediatric Critical Care Research Group
PEEP	Positive End Expiratory Pressure
PICU	Paediatric Intensive Care Unit
SpO_2	Transcutaneous Oxygen saturation
WHO	World Health Organisation

Key Words:
Paediatric, Children, Respiratory Disease, Respiratory Support, Oxygen Therapy

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ABSTRACT

Introduction: Acute hypoxemic respiratory failure (AHRF) in children is the most frequent reason for non-elective hospital admission. During the initial phase, AHRF is a clinical syndrome defined by an oxygen requirement and caused by pneumonia, lower respiratory tract infections, asthma or bronchiolitis. Up to 20% of these children with AHRF can rapidly deteriorate requiring non-invasive or invasive ventilation. Nasal high flow (NHF) therapy has been used by clinicians for oxygen therapy outside intensive care settings to prevent escalation of care. A recent randomised trial in infants with bronchiolitis has shown that NHF therapy reduces the need to escalate therapy. No similar data is available in the older children presenting with AHRF. In this study we aim to investigate in children aged 1-4 years presenting with AHRF if early NHF therapy compared to standard-oxygen therapy reduces hospital length of stay and if this is cost-effective compared to standard treatment.

Methods and Analysis: The study design is an open-labelled randomised multi-centre trial comparing early NHF and standard-oxygen therapy. Children aged 1-4 years (n=1512) presenting with AHRF to one of the participating emergency departments will be randomly allocated to NHF or standard-oxygen therapy once the eligibility criteria have been met (oxygen requirement with transcutaneous saturation <92%/90%, diagnosis of AHRF, admission to hospital and tachypnoea ≥35 breaths/min). Children in the standard-oxygen group can receive rescue NHF therapy if escalation is required. The primary outcome is

hospital length of stay. Secondary outcomes will include length of oxygen therapy, proportion of intensive care admissions, health care resource utilisation and associated costs. Analyses will be conducted on an intention to treat basis.

Ethics and dissemination: Ethics approval has been obtained in Australia (HREC/15/QRCH/159) and New Zealand (HDEC 17/NTA/135). The trial commenced recruitment in December 2017. The study findings will be submitted for publication in a peer-reviewed journal.

Strengths and limitations of this study:

- This study is a pragmatic approach to test the efficacy of nasal high-flow therapy in children with acute hypoxemic respiratory failure.
- This study investigates if early use of nasal high-flow therapy compared to late or rescue nasal high-flow therapy is superior in regards to a patient centred primary outcome; the hospital length of stay.
- The study is performed in a wide variety of hospital settings including regional, metropolitan and tertiary hospitals; hence results will be highly generalisable.
- Blinding of the intervention is not possible, due to the visual differences between the two trial interventions.

INTRODUCTION

Of the 6.3 million children under the age of five years worldwide who died in 2013, over 1 million deaths were caused by acute respiratory infections causing acute hypoxemic respiratory failure (AHRF) (1). In less well-resourced settings, children with severe pneumonia have a mortality rate between 13-20% and most deaths occurring with hypoxemia before therapeutic benefit of antimicrobials (2, 3). While the paediatric mortality due to respiratory infections has decreased in high-income countries, AHRF is the most frequent cause of hospital admission resulting in major consumption of healthcare resources (4-6). Asthma, pneumonia and bronchiolitis associated hospitalisations in children in the USA are estimated to account for over USD $3 billion of costs per year (4). There is an emerging trend to improve respiratory gas exchange with methods other than oxygen, particularly in the early stage of disease process aiming to prevent the progression of the disease (7).

However, to date, the provision of positive pressure ventilation has been restricted to intensive care settings, which remains costly, is a limited resource and requires technical expertise. In view of the global burden of respiratory disease the World Health Organization recognizes oxygen as a potential life-saving treatment and is advocating to develop low cost and low technology oxygen delivery methods that can be delivered in most health care settings (8). Currently, standard oxygen therapy is delivered either using nasal prongs with low flow oxygen up to 4 L/min or using a face mask with oxygen flows of up to 8L/min. Nasal high flow (NHF) therapy is a new promising mode of respiratory support applied as an alternative to non-invasive ventilation, a potentially less tolerated respiratory support (4, 9). NHF therapy can be used very early in the disease process and requires little cooperation by

the child. Several studies have shown that NHF therapy creates a distending pressure of the lung with a PEEP effect of approximately 4-6 cmH_2O using flow rates of 1.5-2 L/kg/min in infants <12 months of age (10). NHF therapy also decreases the work of breathing (10-13). Because of its easy application and the fact that little cooperation of the patient is needed, NHF therapy in emergency departments (ED) has become increasingly popular (14-18). However, the data remains equivocal. A recent randomised controlled trial (RCT) using NHF therapy in adult patients with acute hypoxic respiratory failure (AHRF) showed that NHF therapy compared to standard-oxygen therapy or non-invasive ventilation resulted in reduced mortality in the ICU and at 90 days (19). Yet meta-analysis, including this study, failed to show any definitive benefit for treatment failure or in-hospital mortality (20).

The recent multi-centre PARIS RCT performed in Australia and New Zealand showed that NHF therapy in infants with bronchiolitis (aged < 12months) had a lower failure rate of 12% compared to standard-oxygen with 23% failure rate (21-22). In this study performed in EDs and paediatric wards in general hospitals or tertiary children's hospitals, no difference in the overall hospital length of stay or ICU admission rate was observed. These results are supported by an earlier single-centre RCT in patients with bronchiolitis which also found a lower failure rate with NHF, but no difference in hospital length of stay or length of oxygen treatment (23).

In a recent pilot study, we tested the feasibility of using NHF therapy in 552 children presenting with AHRF (excluded were infants with bronchiolitis <12 months of age). Included were children aged 0-16 years presenting with AHRF (SpO_2 <92%) to the ED and requiring hospital admission. The majority of children (79%) presenting with AHRF were

aged between 1-4 years. Of these children allocated to early NHF therapy, 12% required escalation of care compared to 17 % of children allocated to standard-oxygen therapy (data to be published). The data suggests that there is a beneficial role of NHF therapy in children with AHRF. Due to a lack of high-grade evidence we designed the PARIS 2 study, a randomised multi-centre RCT to test the hypothesis that children with AHRF on NHF therapy as a first line oxygen therapy have a reduced hospital length of stay compared with children on standard-oxygen therapy. We also aim to investigate whether this leads to a reduced requirement for escalation of care. A within trial health economics evaluation will be performed to determine the cost-effectiveness of the intervention, considering the heterogeneity of service users, health system, geographical and economic conditions and end implications for resource allocation from the payer's perspective. The modelling will account for the opportunity cost and affordability of the health system payer. In addition, a decision analytic model will be developed to account for longer term cost-effectiveness modelling.

Aim and Objectives

The PARIS 2 trial will investigate if the use NHF therapy in children presenting with AHRF will reduce the hospital length of stay. This will be achieved by comparing the use of early NHF therapy with standard-oxygen therapy.

The primary objective is to demonstrate if early use of NHF reduces the hospital length of stay.

The secondary objectives are to demonstrate if early use of NHF reduces the requirement to escalate therapy, reduces transfers to higher level of care such as intensive, reduces the proportion of adverse events, to demonstrate ex post within-trial and ex ante longer term cost-effectiveness of high-flow therapy, to show reduced length of oxygen therapy and to ascertain comfort levels of children on high-flow.

METHODS

Study Design and Settings

The PARIS 2 trial is a multi-centre, randomised trial recruiting 1512 children aged 1-4 years requiring hospital admission for AHRF. The study will be performed in EDs (ED) and general paediatric wards of metropolitan hospitals and tertiary children's hospitals in Australia and New Zealand.

Participants

Children will be identified and recruited by treating clinicians in the ED of the participating hospitals. All patients with AHRF (acute respiratory disease and oxygen requirement) in these locations will be screened for inclusion criteria in the study. Patients meeting all inclusion criteria and no exclusion criteria (Table 1) are eligible for randomisation.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Children aged 1 - 4 years plus 364 days presenting with AHRF • *and* require hospital admission despite	• Oxygen requirement and therapy in the emergency department existed for longer than 4 hours prior to

initial assessment and therapy • *and* an ongoing oxygen requirement (SpO_2 <90/92% in room air) at the time of randomisation – observe patient in room air for up to 10 mins if safe to do so to confirm eligibility • *and* have a persistent tachypnoea of ≥ 35 breath/min for ≥10mins at the time of randomisation	inclusion (excludes oxygen given in ambulance or other hospital) • Previous use of high-flow during this illness episode • Upper airway obstruction • Craniofacial malformations • Critically ill infants requiring immediate higher level of respiratory support i.e. non-invasive or invasive ventilation, low level of consciousness *OR* • Critically ill with immediate need for intubation or non-invasive ventilation with the need of closer observation in ICU • Basal skull fracture • Trauma • Cyanotic Heart Disease (eg. Blue baby, expected normal saturation in room air <90/92%) • Home Oxygen therapy • Palliative Care • Cystic Fibrosis

	• Oncology • Child Protection patients

AHRF, acute hypoxemic respiratory failure; ICU, intensive care unit; SpO_2, oxygen saturation.

Consent and Ethical Considerations

One of the primary challenges in performing research in an emergency setting is the inability to obtain true informed consent. Frequently, parents and guardians are not initially available when their child is brought into the ED. Furthermore, when parents or guardians are present, they are often too distressed by the situation to comprehend study procedures and there is not enough time to obtain informed consent (24-26). In all participating centres, prospective consent will be obtained from the parent or guardian where possible. When prospective consent is not possible or practical, and local legislation allows, patients will be randomised to the study and written informed consent to remain in the study will be sought from parents and guardians at the earliest possible time after emergency stabilisation of the child (consent-to-continue). Data for children whose parents and guardians do not wish for their child to remain in the study will be handled according to local hospital policies, and the data will not be available for analysis.

This study has ethical approval for consent-to-continue for participating Australian sites by the Children's Health Queensland Human Research Ethics Committee (HREC/15/QRCH/159) and Ethics Committee of The University of Queensland (2016001491). For sites in New Zealand approval has been received for prospective consent (Health and Disability Ethics Committee, 17/NTA/135) as the legislation of New Zealand does not allow delayed consent.

Definitions

AHRF is defined as children presenting to ED with increased work of breathing due to respiratory disease, having an ongoing oxygen requirement to maintain SpO_2 ≥90/92% (dependent on hospitals' current threshold for administering oxygen) with increased respiratory rate >35 breaths/min, and requiring hospital admission. The syndrome of AHRF represents an array of clinical diagnoses such as pneumonia, pneumonitis, acute lower respiratory tract infection, reactive airways (asthma) including small numbers with bronchiolitis older than 12 months of age. For the purpose of this study there will be two groups of patients investigated with a ***pragmatic and point of care definition,*** which includes clinically diagnosed: a.) *wheeze* (*obstructive) and reactive airway disease* with an oxygen requirement; and b.) *absent wheeze (non-obstructive) and parenchymal lung disease* with an oxygen requirement during hospital admission (Table 2).

Table 2: Clinical definitions for AHRF diagnostic groups

Diagnostic groups: *Obstructive Airway Disease*	**Symptoms**
○ Asthma ○ Reactive Airways Disease ○ Bronchiolitis for children >12 months	Oxygen requirement *AND/OR* ○ wheeze and/or cough ○ +/- viral illness ○ increased work of breathing and respiratory rate (>35/min) ○ +/- fever
Diagnostic groups: *Non-Obstructive Airway Disease*	**Symptoms**
○ Pneumonia – viral or bacterial ○ Aspiration ○ Acute lower respiratory tract infection ○ Bronchopneumonia ○ Acute respiratory distress syndrome ○ Pneumonitis	Oxygen requirement *AND* ○ cough ○ +/- viral illness ○ increased respiratory rate (>35/min) ○ +/- fever

Recruitment, Randomisation and Blinding

Children 1-4 (4 years and 364 days) years of age with respiratory disease will be screened at the time of admission to hospital for presence of inclusion criteria. Identified patients will be treated initially as per the treating clinician for suspected underlying potential cause of AHRF which may include bronchodilator therapy for reactive airway disease, fluid bolus and

other medications such as antibiotics. If AHRF (SpO_2 <90/92% in room air) symptoms persist and hospital admission is required, then the patient will become eligible and will be randomised to standard-oxygen or NHF therapy. Excluded are children as per Table 1. The study protocol prescribes the oxygen delivery and weaning method only (standard-oxygen or NHF therapy). A web-based randomisation schedule will be used with patients allocated 1:1. Randomisation will be stratified by site and by obstructive and reactive airway disease versus non-obstructive and parenchymal lung disease as defined by the admitting clinician.

Interventions and protocol

Treatment protocol for NHF therapy: NHF is set according to weight (Table 3) using the AIRVO-2™ system (Fisher & Paykel Healthcare (FPH) New Zealand). For children presenting with SpO_2 between 85 to 89/91% inclusive, the FiO_2 is initially set at 0.21 and SpO_2 observed for ten minutes. If SpO_2 remains <90/92% after ten minutes then FiO_2 is increased and titrated to achieve SpO_2 ≥90/92%. If SpO_2 has improved to ≥90/92% then NHF therapy is continued in room air. For children presenting with SpO_2 <85% the FiO_2 is immediately increased to achieve SpO_2 ≥90/92%. FiO_2 is adjusted for all children to achieve and maintain SpO_2 of 90/92-98% avoiding long periods of hyperoxia with SpO_2 of 100%. For any flow rates >25 L/min the high-flow rates are increased gradually over two minutes and the patient observed in terms of his/her ability to tolerate NHF therapy. Age and flow specific nasal cannulas will be used.

Table 3. Applied nasal high-flow rates

Weight	High Flow rates

0-12 kg	2L/kg/min Max 25 L/min
13-15 kg	30L/min
16-30 kg	35L/min
31-50 kg	40L/min
>50 kg	50L/min

Treatment protocol standard-oxygen: Standard subnasal 100% oxygen is offered at a rate of up to a maximum of 2 L/min (humidification according to standard hospital practice can occur) or via a face mask with a maximum of 8L/min and oxygen flow rates titrated to achieve SpO_2 of 90/92-98%.

The study design is only prescriptive for the oxygen delivery method. For the remaining respiratory management, the individual hospital internal protocols will be followed, including pharmacological management such as antibiotic or antiviral therapy. Infants and children who are admitted because of increased work of breathing or feeding difficulty but develop an oxygen requirement after admission to the paediatric ward are still eligible for the study.

Step-by-step guide to commence treatment arm – NHF therapy or standard-oxygen

- At the time of randomisation the clinician must be reassured that the patient has SpO_2 <90/92% in room air for preferably up to 10 mins of observational period
- *NHF intervention arm:* Appropriately sized high-flow nasal cannula will used with a gas mixture and flow according to the Table 2. Initially the gas mixture is set at a FiO_2 of 21% and increased if SpO_2 remains <90/92% after ten minutes of NHF therapy. If SpO_2 is <85% at enrolment then FiO_2 is immediately increased to achieve SpO_2 ≥90/92%. If the FiO_2 is greater than 40% (or up to 60% for no longer than 30 minutes and only used if needed from when NHF therapy first initiated) and increased work of breathing is present then a consultation with specialist paediatric center or local intensive care service must occur at this time.
- The disposition of the study participant is dependent on local patient flow. No distinction in nursing ratio and care should be made between the two study arms.
- For the duration of bronchodilator administration, the NHF therapy is stopped and standard-oxygen therapy provided
- *Control intervention arm:* Standard-subnasal oxygen (humidification optional) or face mask oxygen will be offered according to local practice. Maximal flow rates as follows: subnasal oxygen up to a maximum of 2 L/min and face mask oxygen up to 8L/min. If SpO_2 remains <90/92% and/or the work of breathing is further increased since oxygen therapy commenced, then a consultation with a specialist paediatric centre or local intensive care service must occur at this time.
- Observations: Respiratory and heart rate and other clinical parameters hourly as a minimum (or according to hospital policy) and according to the Early Warning Tool (EWT) chart used in the participating study centre

- Weaning off NHF therapy: Only FiO_2 is reduced to maintain SpO_2 ≥90/92-98%. FiO_2 can be reduced to room air (21%). Once stable on room air NHF therapy can be stopped. At least one set of observations showing stable in room air must occur prior to the NHF therapy being stopped. If SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 minutes, and only increase FiO_2 when SpO_2 remains <90/92%. For the patient who starts and remains on room air only (21%) there are at least 2 hours of observations provided prior to stopping the NHF therapy. Again, if SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 minutes, and only increase FiO_2 when SpO_2 remains <90/92%.

The study design is only prescriptive for the oxygen delivery method. For all other respiratory management, the individual hospital internal protocols will be followed, including pharmacological management.

Feeding whilst on NHF therapy. A nasogastric tube (NGT) is not mandatory in the use of NHF therapy but it is encouraged in the patients aged less than 2-3 years if clinically indicated. Insertion of a NGT remains at the discretion of the attending clinician. In patients who do not receive a NGT and are stable and wish to breast feed/drink and/or eat, the NHF therapy should be reduced to 2L/min (low flow therapy) via the same nasal cannula. This can be achieved by decreasing the flow to 2L/min and increasing the oxygen to 95% FiO_2 for a maximum of up to 20 minutes and then return the patient to the previous NHF therapy settings. Patients who have had a NGT inserted should be assessed as to whether they can be fed. The use of the NGT over oral feeding whilst a nasogastric tube is *in situ* is preferred to prevent the risk of aspiration. Nasogastric feeding can be bolus or continuous at the

discretion of the attending physician. Many of these patients will have an intravenous line *in situ*. Children who do not tolerate nasogastric feeds will have intravenous hydration.

Use of nebuliser and/or inhalation burst therapy for NHF therapy patients. For the duration of inhalation/burst therapy, the NHF therapy will be stopped and nasal prongs removed (leaving wiggle pads *in situ* if applied) and administer the burst/inhalation therapy administered. This will allow for greater face-mask seal with the metered dose inhaler (MDI) via spacer if used. For nebulisers there is no need for additional oxygen via nasal prongs. After the inhalation/burst therapy is complete NHF therapy will be returned with previous settings.

Escalation of care with or without change in therapy in both intervention arms (Figure 1). If at any time there is a change in oxygen therapy (standard-oxygen to NHF therapy or NHF therapy to standard-oxygen) data on reasoning for the change in therapy will be captured. Similarly, if there is an escalation of care to intensive care or high dependency unit the clinical criteria will be recorded to inform the decision-making process.

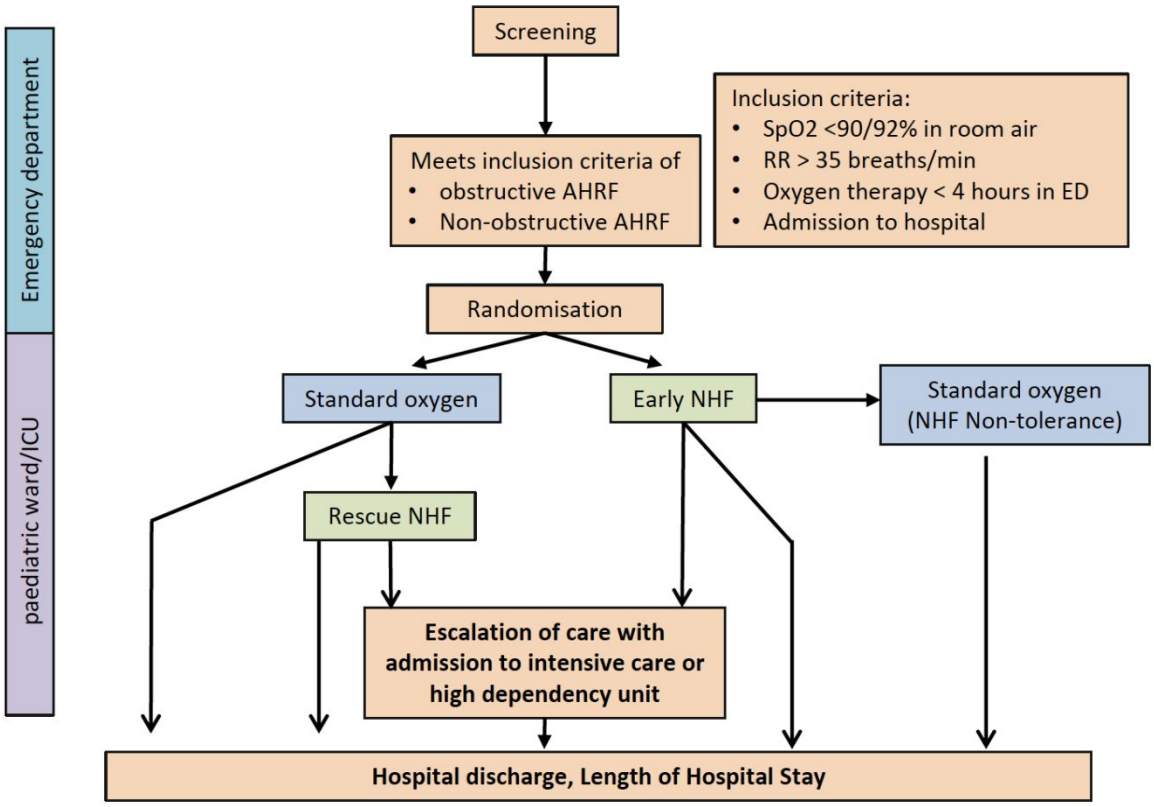

Figure 1. Study flow diagram. AHRF, acute hypoxemic respiratory failure; NHF, nasal high-flow; ICU, intensive care unit; RR, respiratory rate; SpO_2, oxygen saturation; ED, emergency department.

Study Outcomes and Definitions

Primary outcome is defined as the hospital length of stay (days) defined from admission to hospital (time of randomisation) to the time of discharge.

The secondary outcomes are:

1. Length of oxygen therapy
2. Receiving a change in oxygen therapy in general ward settings
3. Intensive care/high dependency care admission
4. Health care cost-effectiveness
5. Transfer to a tertiary hospital
6. Escalation of therapy such as non-invasive or invasive ventilation
7. Tolerance level of NHF therapy compared with standard-oxygen therapy
8. Clinical triggers that result in a change of therapy
9. Complications, serious adverse events (death before hospital discharge, cardiac arrest, pneumothorax or air leak syndrome

A pre-planned sub-analysis on the obstructive and non-obstructive groups to determine which, if any group responds differently to the two treatment arms.

Additionally, a pre-planned sensitivity analysis will be performed using clinical criteria for the primary and secondary outcomes. They are as follows:

a.) heart rate remains >160/min for longer than 2 hours

b.) respiratory rate remains >45/min for longer than 2 hours

c.) oxygen requirement in NHF therapy arm exceeds FiO_2 > 40/50% (dependant on hospital standard policy) to maintain SpO_2 ≥90/92% or oxygen requirement in control oxygen arm exceeds standard oxygen therapy (2 L/min by nasal prong, or 8L/min by face mask) to maintain SpO_2 ≥90/92%

d.) the hospital internal Early Warning Tool (EWT) calls for medical review

Clinical Tolerance for NHF therapy treatment arm**.** It is recognised that NHF therapy is a relatively new therapy for children with mild to moderate severity of respiratory illnesses. The tolerance level of placing nasal cannula with high flows in younger children, particularly the 1-4 year age group, is unknown. This RCT aims to additionally investigate the tolerance level of NHF therapy. A 100mm unmarked visual analogue scale (VAS) will be used as a measurement instrument. Both the parent and the nurse caring for the patient will separately assess the intensity of respiratory patient-comfort level twice during admission: firstly, at one-hour post commencement of oxygen therapy and secondly between 4-48 hours post commencement of oxygen therapy and document the comfort score that they believe the child is experiencing at that point in time. One end of the scale is marked with "no discomfort" and the other end marked as "maximal imaginable discomfort". The VAS will measure both standard-oxygen therapy and NHF therapy treatment arms for level of comfort.

Data Management

Study data will be obtained either directly from hospital records, electronic medical records or copies and entered after verification into the clinical research form (CRF). The

investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All CRF and study documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The document/forms will be stored and locked away as per site specific requirements and regulations for each individual hospital. Ongoing surveillance and adherence to the study protocol will be monitored by the Coordinating Principal Investigator and the steering committee, who are meeting via teleconference at 3-monthly interval. All serious adverse events, protocol deviations and protocol violations will be submitted to the chief investigator and all serious adverse events and protocol violations will be submitted to the approving HREC and local RGOs. All local regulatory process will be followed to ensure adherence to local governance requirements. An independent Data and Safety Monitoring Board (DSMB) that has been used in the past for other respiratory trials will be used. The DSMB will consist of an experienced DSMC Chair, clinical expert, statistician and a secretariat. An interim analysis will be undertaken by the DSMB after 100 participants have been enrolled into the study but only analysed for safety aspects. This had already occurred at the time of the publication of this protocol and the DSMB recommended to continue the trial.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN (SAP)

Sample size. The sample size calculation is based on a two-sided, randomised, parallel group trial design with total length of hospital stay as the primary outcome and survival analysis as the primary method of analysis. We consider a difference in length of hospital stay of at least half a day as clinically meaningful, however for the sample size calculation this will be reduced to 0.4 day to increase the sample size to adjust for the effect of clustering.

Assuming a median length of hospital stay in the control therapy arm of two days (based on pilot data), compared with a median length of hospital stay in the NHF arm of 1.6 days, 5% level of significance and 90% power we require 1209 children. To allow for up to 20% non-compliance we require 1512 children in total; 756 in each treatment group. We estimate a 50-80% enrolment rate of eligible patients.

Statistical analysis plan. Descriptive statistics will be used to report on the baseline characteristics of the total study cohort stratified by treatment group. Kaplan-Meier plots will be used to graphically describe and compare the primary outcome (length of hospital stay) as well as duration of oxygen therapy. Analyses of secondary binary outcomes will be based on chi-squared test for proportions and the absolute difference between treatment groups will be reported as the risk difference with a 95% confidence interval. An independent samples t-test will be used for normally distributed continuous measures; Mann-Whitney U test for non-normally distributed continuous outcomes. Exploratory analyses will be conducted on the subset of patients who require escalation of treatment. These are conditional analyses that are not based on comparing complete randomised groups hence caution will be used needed when interpreting the results. We also plan to compare length of ICU stay between treatment groups for the subgroup of patients that are admitted to ICU. All analyses will be by intention-to-treat. Statistical significance is set at the 0.05 level.

Health economics evaluation. We will build an ex-ante longer term decision analytical model and also undertake ex-post within-trial modelling, to determine the cost-effectiveness of treatment compared to usual care. An appropriate bepoke health economics data collection tool will be developed to provide critical data for these models.

Unit costs will be extracted from standard sources. To provide longer-term analysis, we will build a bespoke Decision Analytical Model to estimate cost-effectiveness under the horizon of 5 years. The model will be based on both aggregate resource, cost use and health state transitions data from literature, expert opinion, along with our newly collected data in the RCT. Models will include sensitivity analysis, and outputs will include Cost Effectiveness Acceptability Curves (CEAC) – these will display the probability of cost-effectiveness at varying thresholds of net monetary benefit (NMB). Following a Markov Chain modelling approach, we will use Monte Carlo simulation methods to incorporate the occurrence and timing of events. The main issue with such ex-ante evaluation is uncertainty, and we will use standard bootstrap methods to account for this in our estimates. This will provide us with a sensitivity analysis of differences in potential costs depending on demographics and socio-economic status. The model will be constructed and continuously updated with new data as it becomes available throughout the project. A standard within-trial cost utility analysis will be undertaken under the horizon of 5 days. This will compare costs and benefits in terms of resource use and quality adjusted life years (QALY) gained. Resource use and travel data will be collected with the bespoke tool and the collated unit costs will be assigned to the resource utilization to provide overall costs for both arms of the trial. Benefits will be assessed using appropriate quality of life instruments, e.g. EQ5D-5L and PEDSql. The analysis will be from the health care provider perspective but with an additional societal perspective, to include for example, consumer travel costs. Probability sensitivity analysis will be provided to give the probability of cost-effectiveness at each threshold level of net monetary benefit. The data from this trial will then feed into our Decision model, enhancing the model further with current and comparable data.

Dissemination

Results will be published in a peer review journal and presented at relevant conferences. Authorship of all publications will be decided by mutual consensus of the research team.

Outcomes and Significance

Providing the hypothesis of the study can be proven, the following impact on future health care is expected: i.) Reduction in hospital length of stay for patients aged 1 to 4 years with AHRF, ii.) Reduction of transfers of patients aged 1 to 4 years with AHRF to specialist paediatric centres - 'keeps patients in their regional hospitals' and potentially gives the regional centres more autonomy in managing their patients with best respiratory practice, iii.) That early intervention reduces the number of patients requiring escalation of treatment, iv.) Reduction in health care costs and demonstration of cost-effectiveness of NHF therapy, v.) Potential to expand NHF therapy to older children with AHRF, vi.) Greater expansion of knowledge for nursing and medical staff on the use of NHF therapy and the benefits and non-benefits in this population of children, vii.) Informing the use of HNF therapy in less developed countries in this population of children and viii.) Development of strategies to implement NHF therapy safely in the described study population.

Current status of the trial

The study enrolment has commenced with 451 children recruited by Oct 2018, and we are expecting 14 centres to be recruiting by end of December 2018.

Sites involved in the study include:

Australia

Queensland

Queensland Children's Hospital

Gold Coast University Hospital

Caboolture Hospital

Ipswich Hospital

Redcliffe Hospital

Townsville Hospital

The Prince Charles Hospital

New South Wales

John Hunter Children's Hospital

Victoria

Royal Children's Hospital Melbourne

Monash Children's Hospital

Western Australia

Perth Children's Hospital

New Zealand

Starship Children's Health

KidzFirst, Middlemore Hospital

Waikato Hospital

DISCUSSION

This large multi-centre randomised trial will provide the much-needed high grade evidence of the efficacy of NHF therapy compared to standard-oxygen in the ARHF children aged 1-<5years. This study will also provide a unique opportunity to investigate the safety profile

off high-flow in children with acute hypoxemic respiratory failure. We will capture data on health resource use and quality of life and the results can be utilized to inform best practice in use of high-flow outside intensive care settings.

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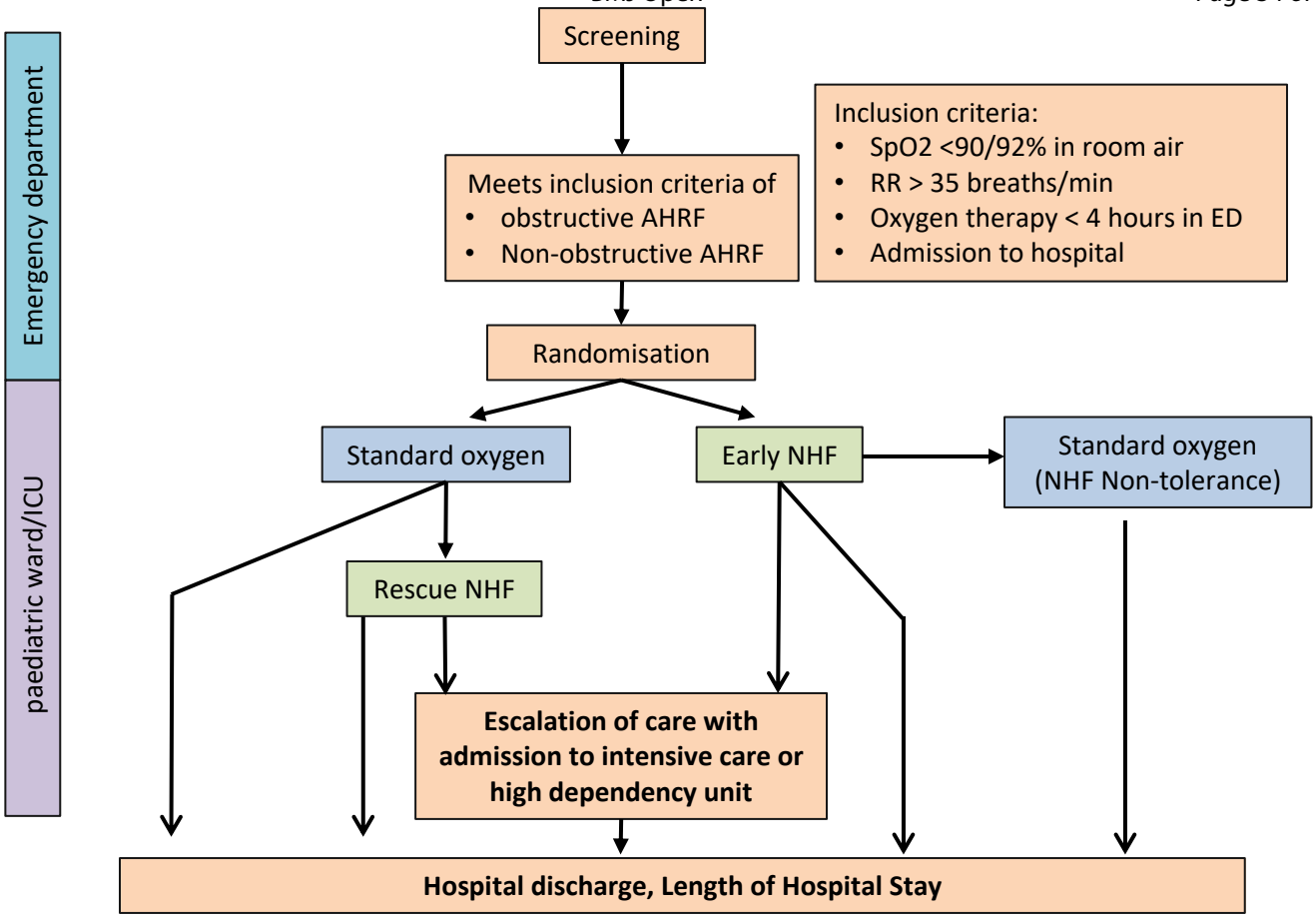
Emergency department
paediatric ward/ICU
Screening
Meets inclusion criteria of
• obstructive AHRF
• Non-obstructive AHRF
Inclusion criteria:
• SpO2 <90/92% in room air
• RR > 35 breaths/min
• Oxygen therapy < 4 hours in ED
• Admission to hospital
Randomisation
Standard oxygen
Early NHF
Standard oxygen
(NHF Non-tolerance)
Rescue NHF
Escalation of care with admission to intensive care or high dependency unit
Hospital discharge, Length of Hospital Stay

BMJ Open

Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial
A Paediatric Acute Respiratory Intervention Study (PARIS 2)

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Title Page

Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial

A Paediatric Acute Respiratory Intervention Study (PARIS 2)

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Roles and Responsibilities:

Trial Registration:

This trial is registered in the Australian New Zealand Clinical Trial Registry ACTRN12618000210279. Due to a clerical error on behalf of the Australian Clinical Trial Registry, the study registration reads as a retrospective registration, which has been acknowledged in writing by the ACTR.

Author contributions:

DF, AS, DS, SD and FEB were responsible for identifying the research question and contributing the drafting of the protocol. All Authors, including DF, AS,DS, FEB, LJS, EO, MLB, TB, SG, SC, JN, VG, MW, JA, HM, AW, JM, JFF, SM, JG, JW, SH, RF, SG, BG, KG have contributed to the development of the protocol and study design. DF was responsible for drafting this manuscript, with comments and feedback from all other authors. KG provided expert statistical advice and input, BG developed the health economic measures and analysis. All authors attest to having approved the final manuscript. DF and AS take responsibility for the manuscript as a whole.

Competing interests:

DF, SG, AS and SD received travel support from Fisher and Paykel Healthcare. All other authors have no conflicts to disclose. Fisher and Paykel have provided equipment and consumables for the study but have had no input in the study design.

Patient consent for publication: Not required

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Steering Committee:

Each site is represented by at least one member for the steering group.

Data and Safety Monitoring Board (DSMB):

Phil Sargent, Scott Burgess, Kristen Gibbons (stat).

Ethics approval: The study protocol has been reviewed and approved by ethics committees in Australia (Children's Health Queensland Human Research Ethics Committee, HREC/15/QRCH/159 and Ethics Committee of The University of Queensland 2016001491) and New Zealand (Health and Disability Ethics Committee HDEC 17/NTA/135).

Key Words:
Paediatric, Children, Respiratory Disease, Respiratory Support, Oxygen Therapy

ABBREVIATION	TERM
AHRF	Acute Hypoxic Respiratory Failure
BiPAP	Bi-level Positive Airway Pressure
CEWT	Children's Early Warning Tool
CPAP	Continuous Positive Airway Pressure
CRF	Clinical Research Form
ED	Emergency Department
EWT	Early Warning Tool
Fi02	Fraction of Inspired Oxygen
FPH	Fisher & Paykel Healthcare
FRC	Functional Residual Capacity
ICU	Intensive Care Unit
LCCH	Lady Cilento Children's Hospital
MDI	Metered Dose Inhaler
MET	Medical Emergency Team
NGT	Nasogastric Tube
NHF	Nasal High Flow
NIV	Non-Invasive Ventilation
PCCRG	Paediatric Critical Care Research Group
PEEP	Positive End Expiratory Pressure
PICU	Paediatric Intensive Care Unit
SpO_2	Transcutaneous Oxygen saturation
WHO	World Health Organisation

Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial

A Paediatric Acute Respiratory Intervention Study (PARIS 2)

ABSTRACT

Introduction: Acute hypoxemic respiratory failure (AHRF) in children is the most frequent reason for non-elective hospital admission. During the initial phase, AHRF is a clinical syndrome defined for the purpose of this study by an oxygen requirement and caused by pneumonia, lower respiratory tract infections, asthma or bronchiolitis. Up to 20% of these children with AHRF can rapidly deteriorate requiring non-invasive or invasive ventilation. Nasal high flow (NHF) therapy has been used by clinicians for oxygen therapy outside intensive care settings to prevent escalation of care. A recent randomised trial in infants with bronchiolitis has shown that NHF therapy reduces the need to escalate therapy. No similar data is available in the older children presenting with AHRF. In this study we aim to investigate in children aged 1-4 years presenting with AHRF if early NHF therapy compared to standard-oxygen therapy reduces hospital length of stay and if this is cost-effective compared to standard treatment.

Methods and Analysis: The study design is an open-labelled randomised multi-centre trial comparing early NHF and standard-oxygen therapy and will be stratified by sites and into obstructive and non-obstructive groups. Children aged 1-4 years (n=1512) presenting with AHRF to one of the participating emergency departments will be randomly allocated to NHF or standard-oxygen therapy once the eligibility criteria have been met (oxygen requirement with transcutaneous saturation <92%/90% (dependant on hospital standard threshold),

diagnosis of AHRF, admission to hospital and tachypnoea ≥35 breaths/min). Children in the standard-oxygen group can receive rescue NHF therapy if escalation is required. The primary outcome is hospital length of stay. Secondary outcomes will include length of oxygen therapy, proportion of intensive care admissions, health care resource utilisation and associated costs. Analyses will be conducted on an intention to treat basis.

Ethics: Ethics approval has been obtained in Australia (HREC/15/QRCH/159) and New Zealand (HDEC 17/NTA/135). The trial commenced recruitment in December 2017.

Dissemination:

The study findings will be submitted for publication in a peer-reviewed journal and presented at relevant conferences. Authorship of all publications will be decided by mutual consensus of the research team.

Strengths and limitations of this study:

- This study is a pragmatic approach to test the efficacy of nasal high-flow therapy in children with acute hypoxemic respiratory failure.
- This study investigates if early use of nasal high-flow therapy compared to late or rescue nasal high-flow therapy is superior in regards to a patient centred primary outcome; the hospital length of stay.
- The study is performed in a wide variety of hospital settings including regional, metropolitan and tertiary hospitals; hence results will be highly generalisable.
- Blinding of the intervention is not possible, due to the visual differences between the two trial interventions.

INTRODUCTION

Of the 6.3 million children under the age of five years worldwide who died in 2013, over 1 million deaths were caused by acute respiratory infections causing acute hypoxemic respiratory failure (AHRF) (1). In less well-resourced settings, children with severe pneumonia have a mortality rate between 13-20% and most deaths occurring with hypoxemia before therapeutic benefit of antimicrobials (2, 3). While the paediatric mortality due to respiratory infections has decreased in high-income countries, AHRF is the most frequent cause of hospital admission resulting in major consumption of healthcare resources (4-6). Asthma, pneumonia and bronchiolitis associated hospitalisations in children in the USA are estimated to account for over USD $3 billion of costs per year (4). There is an emerging trend to improve respiratory gas exchange with methods other than oxygen, particularly in the early stage of disease process aiming to prevent the progression of the disease (7).

However, to date, the provision of positive pressure ventilation has been restricted to intensive care settings, which remains costly, is a limited resource and requires technical expertise. In view of the global burden of respiratory disease the World Health Organization recognizes oxygen as a potential life-saving treatment and is advocating to develop low cost and low technology oxygen delivery methods that can be delivered in most health care settings (8). Currently, standard oxygen therapy is delivered either using nasal prongs with low flow oxygen up to 4 L/min or using a face mask with oxygen flows of up to 8L/min. Nasal high flow (NHF) therapy is a new promising mode of respiratory support applied as an alternative to non-invasive ventilation, a potentially less tolerated respiratory support (4, 9). NHF therapy can be used very early in the disease process and requires little cooperation by

the child. Several studies have shown that NHF therapy creates a distending pressure of the lung with a PEEP effect of approximately 4-6 cmH_2O using flow rates of 1.5-2 L/kg/min in infants <12 months of age (10). NHF therapy also decreases the work of breathing (10-13). Because of its easy application and the fact that little cooperation of the patient is needed, NHF therapy in emergency departments (ED) has become increasingly popular (14-18). However, the data remains equivocal. A recent randomised controlled trial (RCT) using NHF therapy in adult patients with acute hypoxic respiratory failure (AHRF) showed that NHF therapy compared to standard-oxygen therapy or non-invasive ventilation resulted in reduced mortality in the ICU and at 90 days (19). Yet meta-analysis, including this study, failed to show any definitive benefit for treatment failure or in-hospital mortality (20).

The recent multi-centre PARIS RCT performed in Australia and New Zealand showed that NHF therapy in infants with bronchiolitis (aged < 12months) had a lower failure rate of 12% compared to standard-oxygen with 23% failure rate (21-22). In this study performed in EDs and paediatric wards in general hospitals or tertiary children's hospitals, no difference in the overall hospital length of stay or ICU admission rate was observed. These results are supported by an earlier single-centre RCT in patients with bronchiolitis which also found a lower failure rate with NHF, but no difference in hospital length of stay or length of oxygen treatment (23).

In a recent pilot study, we tested the feasibility of using NHF therapy in 552 children presenting with AHRF (excluded were infants with bronchiolitis <12 months of age). Included were children aged 0-16 years presenting with AHRF (SpO_2 <92%) to the ED and requiring hospital admission. The majority of children (79%) presenting with AHRF were

aged between 1-4 years. Of these children allocated to early NHF therapy, 12% required escalation of care compared to 17 % of children allocated to standard-oxygen therapy (data to be published). The data suggests that there is a beneficial role of NHF therapy in children with AHRF. Due to a lack of high-grade evidence we designed the PARIS 2 study, a randomised multi-centre RCT to test the hypothesis that children with AHRF on NHF therapy as a first line oxygen therapy have a reduced hospital length of stay compared with children on standard-oxygen therapy. We also aim to investigate whether this leads to a reduced requirement for escalation of care. A within trial health economics evaluation will be performed to determine the cost-effectiveness of the intervention, considering the heterogeneity of service users, health system, geographical and economic conditions and end implications for resource allocation from the payer's perspective. The modelling will account for the opportunity cost and affordability of the health system payer. In addition, a decision analytic model will be developed to account for longer term cost-effectiveness modelling.

Aim and Objectives

The PARIS 2 trial will investigate if the use NHF therapy in children presenting with AHRF will reduce the hospital length of stay. This will be achieved by comparing the use of early NHF therapy with standard-oxygen therapy.

The primary objective is to demonstrate if early use of NHF reduces the hospital length of stay.

The secondary objectives are to demonstrate if early use of NHF reduces the requirement to escalate therapy, reduces transfers to higher level of care such as intensive, reduces the proportion of adverse events, to demonstrate ex post within-trial and ex ante longer term cost-effectiveness of high-flow therapy, to show reduced length of oxygen therapy and to ascertain comfort levels of children on high-flow.

METHODS

Study Design and Settings

The PARIS 2 trial is a multi-centre, randomised trial recruiting 1512 children aged 1-4 years requiring hospital admission for AHRF. The study will be performed in EDs (ED) and general paediatric wards of metropolitan hospitals and tertiary children's hospitals in Australia and New Zealand.

Definitions

AHRF is defined as children presenting to ED with increased work of breathing due to respiratory disease, having an ongoing oxygen requirement to maintain SpO_2 ≥90/92% (dependent on hospitals' current threshold for administering oxygen, which can either be 90% or 92%) with increased respiratory rate >35 breaths/min, and requiring hospital admission. The syndrome of AHRF represents an array of clinical diagnoses such as pneumonia, pneumonitis, acute lower respiratory tract infection, reactive airways (asthma) including small numbers with bronchiolitis older than 12 months of age. For the purpose of this study there will be two groups of patients investigated with a ***pragmatic and point of care definition,*** which includes clinically diagnosed: a.) *wheeze* (*obstructive) and reactive airway disease* with an oxygen requirement; and b.) *absent wheeze (non-obstructive) and parenchymal lung disease* with an oxygen requirement during hospital admission (Table 1).

Table 1: Clinical definitions for AHRF diagnostic groups

Diagnostic groups: *Obstructive Airway Disease*	**Symptoms**
○ Asthma ○ Reactive Airways Disease ○ Bronchiolitis for children >12 months	Oxygen requirement *AND/OR* ○ wheeze and/or cough ○ +/- viral illness ○ increased work of breathing and respiratory rate (>35/min) ○ +/- fever
Diagnostic groups: *Non-Obstructive Airway Disease*	**Symptoms**
○ Pneumonia – viral or bacterial ○ Aspiration ○ Acute lower respiratory tract infection ○ Bronchopneumonia ○ Acute respiratory distress syndrome ○ Pneumonitis	Oxygen requirement *AND* ○ cough ○ +/- viral illness ○ increased respiratory rate (>35/min) ○ +/- fever

Participants

Children will be identified and recruited by treating clinicians in the ED of the participating hospitals. All patients with AHRF (acute respiratory disease and oxygen requirement) in these locations will be screened for inclusion criteria in the study. Patients meeting all inclusion criteria and no exclusion criteria (Table 2) are eligible for randomisation.

Table 2: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Children aged 1 - 4 years plus 364 days presenting with AHRF • *and* require hospital admission despite initial assessment and therapy • *and* an ongoing oxygen requirement (SpO_2 <90/92%* in room air, dependent on hospital policy) • *and* have a persistent tachypnoea of ≥ 35 breath/min for ≥10mins at the time of randomisation	• Oxygen requirement and therapy in the emergency department existed for longer than 4 hours prior to inclusion (excludes oxygen given in ambulance or other hospital) • Previous use of high-flow during this illness episode • Upper airway obstruction • Craniofacial malformations • Critically ill infants requiring immediate higher level of respiratory support i.e. non-invasive or invasive ventilation, low level of consciousness *OR* • Critically ill with immediate need for intubation or non-invasive ventilation with the need of closer observation in ICU • Basal skull fracture • Trauma

	• Cyanotic Heart Disease (eg. Blue baby, expected normal saturation in room air <90/92%) • Home Oxygen therapy • Palliative Care • Cystic Fibrosis • Oncology • Child Protection patients

AHRF, acute hypoxemic respiratory failure; ICU, intensive care unit; SpO_2, oxygen saturation.

Consent and Ethical Considerations

One of the primary challenges in performing research in an emergency setting is the inability to obtain true informed consent. Frequently, parents and guardians are not initially available when their child is brought into the ED. Furthermore, when parents or guardians are present, they are often too distressed by the situation to comprehend study procedures and there is not enough time to obtain informed consent (24-26). In all participating centres, prospective consent will be obtained from the parent or guardian where possible. When prospective consent is not possible or practical, and local legislation allows, patients will be randomised to the study and written informed consent to remain in the study will be sought from parents and guardians at the earliest possible time after emergency stabilisation of the child (consent-to-continue). Data for children whose parents and guardians do not wish for their child to remain in the study will be handled according to local hospital policies, and the data will not be available for analysis.

This study has ethical approval for consent-to-continue for participating Australian sites by the Children's Health Queensland Human Research Ethics Committee (HREC/15/QRCH/159) and Ethics Committee of The University of Queensland (2016001491). For sites in New Zealand approval has been received for prospective consent (Health and Disability Ethics Committee, 17/NTA/135) as the legislation of New Zealand does not allow delayed consent.

Recruitment, Randomisation and Blinding

Children 1-4 (4 years and 364 days) years of age with respiratory disease will be screened at the time of admission to hospital for presence of inclusion criteria. Identified patients will be treated initially as per the treating clinician for suspected underlying potential cause of AHRF which may include bronchodilator therapy for reactive airway disease, fluid bolus and other medications such as antibiotics. If AHRF (SpO_2 <90/92% in room air) symptoms persist and hospital admission is required, then the patient will become eligible and will be randomised to standard-oxygen or NHF therapy. Excluded are children as per Table 2. The study protocol prescribes the oxygen delivery and weaning method only (standard-oxygen or NHF therapy). A web-based randomisation schedule with a block size of ten will be used with patients allocated 1:1 and stratified by site and by obstructive and reactive airway disease versus non-obstructive and parenchymal lung disease as defined by the admitting clinician.

Interventions and protocol

Treatment protocol for NHF therapy: NHF is set according to weight (Table 3) using the AIRVO-2™ system (Fisher & Paykel Healthcare (FPH) New Zealand). For children presenting with SpO_2 between 85 to 89/91% inclusive, the FiO_2 is initially set at 0.21 and SpO_2 observed

for ten minutes. If SpO_2 remains <90/92% after ten minutes then FiO_2 is increased and titrated to achieve SpO_2 ≥90/92%. If SpO_2 has improved to ≥90/92% then NHF therapy is continued in room air. For children presenting with SpO_2 <85% the FiO_2 is immediately increased in 5% increments to achieve SpO_2 ≥90/92%. FiO_2 is adjusted for all children to achieve and maintain SpO_2 of 90/92-98% avoiding long periods of hyperoxia with SpO_2 of 100%. For any flow rates >25 L/min the high-flow rates are increased gradually over two minutes and the patient observed in terms of his/her ability to tolerate NHF therapy. Age and flow specific nasal cannulas will be used.

Table 3. Applied nasal high-flow rates

Weight	**High Flow rates**
0-12 kg	2L/kg/min Max 25 L/min
13-15 kg	30L/min
16-30 kg	35L/min
31-50 kg	40L/min
>50 kg	50L/min

Treatment protocol standard-oxygen: Standard subnasal 100% oxygen is offered at a rate of up to a maximum of 2 L/min (humidification according to standard hospital practice can

occur) or via a face mask with a maximum of 8L/min and oxygen flow rates titrated to achieve SpO_2 of 90/92-98%.

The study design is only prescriptive for the oxygen delivery method. For the remaining respiratory management, the individual hospital internal protocols will be followed, including pharmacological management such as antibiotic or antiviral therapy. Infants and children who are admitted because of increased work of breathing or feeding difficulty but develop an oxygen requirement after admission to the paediatric ward are still eligible for the study.

<u>Step-by-step guide to commence treatment arm – NHF therapy or standard-oxygen</u>

- At the time of randomisation the clinician must be reassured that the patient has SpO_2 <90/92% in room air for preferably up to 10 mins of observational period
- *NHF intervention arm:* Appropriately sized high-flow nasal cannula will used with a gas mixture and flow according to the Table 3. Initially the gas mixture is set at a FiO_2 of 21% and increased if SpO_2 remains <90/92% after ten minutes of NHF therapy. If SpO_2 is <85% at enrolment then FiO_2 is immediately increased to achieve SpO_2 ≥90/92%. If the FiO_2 is greater than 40% (or up to 60% for no longer than 30 minutes and only used if needed from when NHF therapy first initiated) and increased work of breathing is present then a consultation with specialist paediatric center or local intensive care service must occur at this time.
- The disposition of the study participant is dependent on local patient flow. No distinction in nursing ratio and care should be made between the two study arms.
- For the duration of bronchodilator administration, the NHF therapy is stopped and standard-oxygen therapy provided
- *Control intervention arm:* Standard-subnasal oxygen (humidification optional) or face mask oxygen will be offered according to local practice. Maximal flow rates as follows: subnasal oxygen up to a maximum of 2 L/min and face mask oxygen up to 8L/min. If SpO_2 remains <90/92% and/or the work of breathing is further increased since oxygen therapy commenced, then a consultation with a specialist paediatric centre or local intensive care service must occur at this time.
- Observations: Respiratory and heart rate and other clinical parameters hourly as a minimum (or according to hospital policy) and according to the Early Warning Tool (EWT) chart used in the participating study centre

- Weaning off NHF therapy: Only FiO_2 is reduced to maintain SpO_2 ≥90/92-98%. FiO_2 can be reduced to room air (21%). Once stable on room air NHF therapy can be stopped. At least one set of observations showing stable in room air must occur prior to the NHF therapy being stopped. If SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 minutes, and only increase FiO_2 when SpO_2 remains <90/92%. For the patient who starts and remains on room air only (21%) there are at least 2 hours of observations provided prior to stopping the NHF therapy. Again, if SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 minutes, and only increase FiO_2 when SpO_2 remains <90/92%.

The study design is only prescriptive for the oxygen delivery method. For all other respiratory management, the individual hospital internal protocols will be followed, including pharmacological management.

Feeding whilst on NHF therapy. A nasogastric tube (NGT) is not mandatory in the use of NHF therapy but it is encouraged in the patients aged less than 2-3 years if clinically indicated. Insertion of a NGT remains at the discretion of the attending clinician. In patients who do not receive a NGT and are stable and wish to breast feed/drink and/or eat, the NHF therapy should be reduced to 2L/min (low flow therapy) via the same nasal cannula. This can be achieved by decreasing the flow to 2L/min and increasing the oxygen to 95% FiO_2 for a maximum of up to 20 minutes and then return the patient to the previous NHF therapy settings. Patients who have had a NGT inserted should be assessed as to whether they can be fed. The use of the NGT over oral feeding whilst a nasogastric tube is *in situ* is preferred to prevent the risk of aspiration. Nasogastric feeding can be bolus or continuous at the

discretion of the attending physician. Many of these patients will have an intravenous line *in situ*. Children who do not tolerate nasogastric feeds will have intravenous hydration.

Use of nebuliser and/or inhalation burst therapy for NHF therapy patients. For the duration of inhalation/burst therapy, the NHF therapy will be stopped and nasal prongs removed (leaving wiggle pads *in situ* if applied) and administer the burst/inhalation therapy administered. This will allow for greater face-mask seal with the metered dose inhaler (MDI) via spacer if used. For nebulisers there is no need for additional oxygen via nasal prongs. After the inhalation/burst therapy is complete NHF therapy will be returned with previous settings.

Escalation of care with or without change in therapy in both intervention arms (Figure 1). If at any time there is a change in oxygen therapy (standard-oxygen to NHF therapy or NHF therapy to standard-oxygen) data on reasoning for the change in therapy will be captured. Similarly, if there is an escalation of care to intensive care or high dependency unit the clinical criteria will be recorded to inform the decision-making process.

Study Outcomes and Definitions

Primary outcome is defined as the hospital length of stay (days) defined from admission to hospital (time of randomisation) to the time of discharge.

The secondary outcomes are:

1. Length of oxygen therapy since randomisation
2. Receiving a change in oxygen therapy in general ward settings from NHF to standard oxygen therapy (non-tolerance) or from standard oxygen to NHF therapy

3. Intensive care/high dependency care admission
4. Health care cost-effectiveness
5. Transfer to a tertiary hospital
6. Escalation of therapy such as non-invasive or invasive ventilation
7. Tolerance level of NHF therapy compared with standard-oxygen therapy
8. Clinical triggers that result in a change of therapy
9. Complications, serious adverse events (death before hospital discharge, cardiac arrest, pneumothorax or air leak syndrome

A pre-planned sub-analysis on the obstructive and non-obstructive groups to determine which, if any group responds differently to the two treatment arms and within the differing age groups (in one-year steps).

Additionally, a pre-planned sensitivity analysis will be performed using clinical criteria for the primary and secondary outcomes. They are as follows:

a.) heart rate remains >160/min for longer than 2 hours

b.) respiratory rate remains >45/min for longer than 2 hours

c.) oxygen requirement in NHF therapy arm exceeds FiO_2 > 40/50% (dependant on hospital standard policy) to maintain SpO_2 ≥90/92% or oxygen requirement in control oxygen arm exceeds standard oxygen therapy (2 L/min by nasal prong, or 8L/min by face mask) to maintain SpO_2 ≥90/92%

d.) the hospital internal Early Warning Tool (EWT) calls for medical review

Data Measures

Baseline demographics, age, weight, admission and discharge diagnosis, viral and bacterial testing, and medical therapy such as antibiotics/antiviral, steroids, inhaled or intravenous bronchodilators and other drugs will be captured during the entire stay in hospital. Physiological parameters (heart rate, respiratory rate, body temperature, oxygen saturation, work of breathing, comfort scale, oxygen requirement) will be obtained at the time of randomisation and after initiation of the allocated intervention, at any time of change of respiratory support and at time of escalation of care including admission of intensive care. Data on respiratory support provided in intensive care will be obtained. Data on feeding during the study will be also captured.

Clinical Tolerance for NHF therapy treatment arm**.** It is recognised that NHF therapy is a relatively new therapy for children with mild to moderate severity of respiratory illnesses. The tolerance level of placing nasal cannula with high flows in younger children, particularly the 1-4 year age group, is unknown. This RCT aims to additionally investigate the tolerance level of NHF therapy. A 100mm unmarked visual analogue scale (VAS) will be used as a measurement instrument. Both the parent and the nurse caring for the patient will separately assess the intensity of respiratory patient-comfort level twice during admission: firstly, at one-hour post commencement of oxygen therapy and secondly between 4-48 hours post commencement of oxygen therapy and document the comfort score that they believe the child is experiencing at that point in time. One end of the scale is marked with “no discomfort” and the other end marked as “maximal imaginable discomfort”. The VAS will measure both standard-oxygen therapy and NHF therapy treatment arms for level of comfort.

Data Management

Study data will be obtained either directly from hospital records, electronic medical records or copies and entered after verification into the clinical research form (CRF). The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All CRF and study documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The document/forms will be stored and locked away as per site specific requirements and regulations for each individual hospital. Ongoing surveillance and adherence to the study protocol will be monitored by the Coordinating Principal Investigator and the steering committee, who are meeting via teleconference at 3-monthly interval. All serious adverse events, protocol deviations and protocol violations will be submitted to the chief investigator and all serious adverse events and protocol violations will be submitted to the approving HREC and local RGOs. All local regulatory process will be followed to ensure adherence to local governance requirements. An independent Data and Safety Monitoring Board (DSMB) that has been used in the past for other respiratory trials will be used. The DSMB will consist of an experienced DSMC Chair, clinical expert, statistician and a secretariat. An interim analysis will be undertaken by the DSMB after 100 participants have been enrolled into the study but only analysed for safety aspects. This had already occurred at the time of the publication of this protocol and the DSMB recommended to continue the trial.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN (SAP)

Sample size. The sample size calculation is based on a two-sided, randomised, parallel group trial design with total length of hospital stay as the primary outcome and survival analysis as

the primary method of analysis. We consider a difference in length of hospital stay of at least half a day as clinically meaningful, however for the sample size calculation this will be reduced to 0.4 day to increase the sample size to adjust for the effect of clustering. Assuming a median length of hospital stay in the control therapy arm of two days (based on pilot data), compared with a median length of hospital stay in the NHF arm of 1.6 days, 5% level of significance and 90% power we require 1209 children. To allow for up to 20% non-compliance we require 1512 children in total; 756 in each treatment group. We estimate a 50-80% enrolment rate of eligible patients.

Statistical analysis plan. Descriptive statistics will be used to report on the baseline characteristics of the total study cohort stratified by treatment group. Kaplan-Meier plots will be used to graphically describe and compare the primary outcome (length of hospital stay) as well as duration of oxygen therapy. Analyses of secondary binary outcomes will be based on chi-squared test for proportions and the absolute difference between treatment groups will be reported as the risk difference with a 95% confidence interval. An independent samples t-test will be used for normally distributed continuous measures; Mann-Whitney U test for non-normally distributed continuous outcomes. Exploratory analyses will be conducted on the subset of patients who require escalation of treatment. These are conditional analyses that are not based on comparing complete randomised groups hence caution will be used needed when interpreting the results. We plan to compare length of ICU stay between treatment groups for the subgroup of patients that are admitted to ICU. All analyses will be by intention-to-treat. Statistical significance is set at the 0.05 level.

Health economics evaluation. We will build an ex-ante longer term decision analytical model and also undertake ex-post within-trial modelling, to determine the cost-effectiveness of

treatment compared to usual care. An appropriate bepoke health economics data collection tool will be developed to provide critical data for these models. Unit costs will be extracted from standard sources. To provide longer-term analysis, we will build a bespoke Decision Analytical Model to estimate cost-effectiveness under the horizon of 5 years. The model will be based on both aggregate resource, cost use and health state transitions data from literature, expert opinion, along with our newly collected data in the RCT. Models will include sensitivity analysis, and outputs will include Cost Effectiveness Acceptability Curves (CEAC) – these will display the probability of cost-effectiveness at varying thresholds of net monetary benefit (NMB). Following a Markov Chain modelling approach, we will use Monte Carlo simulation methods to incorporate the occurrence and timing of events. The main issue with such ex-ante evaluation is uncertainty, and we will use standard bootstrap methods to account for this in our estimates. This will provide us with a sensitivity analysis of differences in potential costs depending on demographics and socio-economic status. The model will be constructed and continuously updated with new data as it becomes available throughout the project. A standard within-trial cost utility analysis will be undertaken under the horizon of 5 days. This will compare costs and benefits in terms of resource use and quality adjusted life years (QALY) gained. Resource use and travel data will be collected with the bespoke tool and the collated unit costs will be assigned to the resource utilization to provide overall costs for both arms of the trial. Benefits will be assessed using appropriate quality of life instruments, e.g. EQ5D-5L and PEDSql. The analysis will be from the health care provider perspective but with an additional societal perspective, to include for example, consumer travel costs. Probability sensitivity analysis will be provided to give the probability of cost-effectiveness at each threshold level of net monetary benefit. The data from this trial will then feed into our Decision model, enhancing the model further with current and comparable data.

Outcomes and Significance

Providing the hypothesis of the study can be proven, the following impact on future health care is expected: i.) Reduction in hospital length of stay for patients aged 1 to 4 years with AHRF, ii.) Reduction of transfers of patients aged 1 to 4 years with AHRF to specialist paediatric centres - 'keeps patients in their regional hospitals' and potentially gives the regional centres more autonomy in managing their patients with best respiratory practice, iii.) That early intervention reduces the number of patients requiring escalation of treatment, iv.) Reduction in health care costs and demonstration of cost-effectiveness of NHF therapy, v.) Potential to expand NHF therapy to older children with AHRF, vi.) Greater expansion of knowledge for nursing and medical staff on the use of NHF therapy and the benefits and non-benefits in this population of children, vii.) Informing the use of HNF therapy in less developed countries in this population of children and viii.) Development of strategies to implement NHF therapy safely in the described study population.

Limitations

The intervention of high-flow therapy cannot be blinded and a certain clinician driven bias may occur. The escalation of care is driven by clinical criteria and judgment and there is the potential bias to favour one intervention over the other. However, our previous high-flow trial in bronchiolitis showed that this element was not cofounding the study outcomes (22).

Data Sharing.

Data generated by this study will be shared and available in deidentified form upon reasonable request, wherever legally and ethically possible.

Patient and Public Involvement

For the study protocol there was no direct patient or public involvement.

Current status of the trial

The study enrolment has commenced with 451 children recruited by Oct 2018, in and we are expecting 14 centres to be recruiting by end of December 2018.

Sites involved in the study include:

Australia

Queensland

Queensland Children's Hospital

Gold Coast University Hospital

Caboolture Hospital

Ipswich Hospital

Redcliffe Hospital

Townsville Hospital

The Prince Charles Hospital

New South Wales

John Hunter Children's Hospital

Victoria

Royal Children's Hospital Melbourne

Monash Children's Hospital

Western Australia

Perth Children's Hospital

New Zealand

Starship Children's Health

KidzFirst, Middlemore Hospital

Waikato Hospital

DISCUSSION

This large multi-centre randomised trial will provide the much-needed high grade evidence of the efficacy of NHF therapy compared to standard-oxygen in the ARHF children aged 1-<5years. This study will also provide a unique opportunity to investigate the safety profile off high-flow in children with acute hypoxemic respiratory failure. We will capture data on health resource use and quality of life and the results can be utilized to inform best practice in use of high-flow outside intensive care settings.

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LEGENDS

Figure 1.

Study flow diagram. AHRF, acute hypoxemic respiratory failure; NHF, nasal high-flow; ICU, intensive care unit; RR, respiratory rate; SpO_2, oxygen saturation; ED, emergency department.

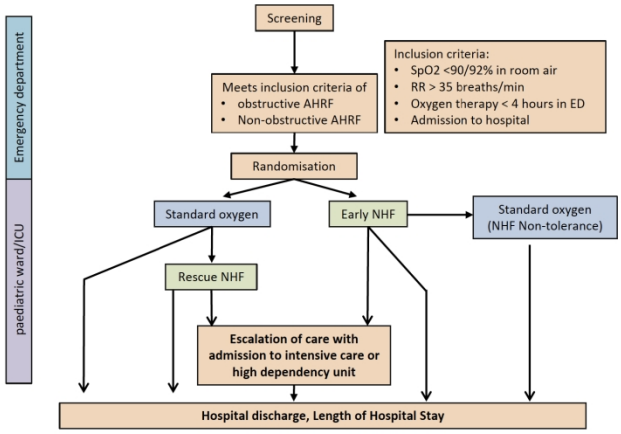

Figure 1. Study flow diagram. AHRF, acute hypoxemic respiratory failure; NHF, nasal high-flow; ICU, intensive care unit; RR, respiratory rate; SpO_2, oxygen saturation; ED, emergency department.

Figure 1. Study flow diagram. AHRF, acute hypoxemic respiratory failure; NHF, nasal high-flow; ICU, intensive care unit; RR, respiratory rate; SpO2, oxygen saturation; ED, emergency department.

209x297mm (233 x 233 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (PAGE 1, 7-8)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry PAGE 4
	2b	All items from the World Health Organization Trial Registration Data Set N/A
Protocol version	3	Date and version identifier VERSION 13.0 DATED 7TH DEC 2019
Funding	4	Sources and types of financial, material, and other support PAGE 5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors PAGE 5
	5b	Name and contact information for the trial sponsor PAGE 5 - NHMRC
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) PAGE 5
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (PAGE 7, 9-11)
	6b	Explanation for choice of comparators (PAGE 11, 16-18)
Objectives	7	Specific objectives or hypotheses (PAGE 11-12)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (PAGE 12-20)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained. PAGE 12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) PAGE 14
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (PAGE 16-19)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) PAGE 22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (PAGE 21-22)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (PAGE 27-28)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (PAGE 24-25)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size N/A
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions PAGE 16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned PAGE 16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions PAGE 16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how NOT DISCUSSED
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (PAGE 23-24)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols NOT DISCUSSED – USE INTERNAL PROCESSES
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (PAGE 23-24)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (PAGE 23-24)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (PAGE 23-24)

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (PAGE 23-24)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (PAGE 5 AND 24)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial PAGE 24
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct PAGE 24
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor NOT DISCUSSED – USE INTERNAL PROCESSES
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval PAGE 5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) NOT DISCUSSED – USE INTERNAL PROCESSES
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (PAGE 15-16)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial PAGE 25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site PAGE 4-5
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (PAGE 15, 23-24)

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation NOT APPLICABLE
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions NOT DISCUSSED
	31b	Authorship eligibility guidelines and any intended use of professional writers. NOT DISCUSSED – USE INTERNAL PROCESSES
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - NOT DISCUSSED – WILL PROVIDE WITH MAIN OUTCOME PUBLICATION
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates NOT PROVIDED
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable NOT DISCUSSED AS NOT REQUIRED.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial
A Paediatric Acute Respiratory Intervention Study (PARIS 2)

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Title Page

Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial

A Paediatric Acute Respiratory Intervention Study (PARIS 2)

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Roles and Responsibilities:

Trial Registration:

This trial is registered in the Australian New Zealand Clinical Trial Registry ACTRN12618000210279. Due to a clerical error on behalf of the Australian Clinical Trial Registry, the study registration reads as a retrospective registration, which has been acknowledged in writing by the ACTR.

Author contributions:

DF, AS, DS, SD and FEB were responsible for identifying the research question and contributing to the drafting of the protocol. All Authors, including DF, AS,DS, FEB, LJS, EO, MLB, TH, SG, SC, JN, VG, MW, JA, HM, AW, JM, JFF, SM, JG, JW, SH, RF, SG, BG, KG have contributed to the development of the protocol and study design. DF was responsible for drafting this manuscript, with comments and feedback from all other authors. KG provided expert statistical advice and input, BG developed the health economic measures and analysis. All authors attest to having approved the final manuscript. DF and AS take responsibility for the manuscript as a whole.

Competing interests:

DF, SG, AS and SD received travel support from Fisher and Paykel Healthcare. All other authors have no conflicts to disclose. Fisher and Paykel have provided equipment and consumables for the study but have had no input in the study design.

Patient consent for publication: Not required

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Steering Committee:

Each site is represented by at least one member for the steering group.

Data and Safety Monitoring Board (DSMB):

Phil Sargent, Scott Burgess, Kristen Gibbons (stat).

Ethics approval: The study protocol has been reviewed and approved by ethics committees in Australia (Children's Health Queensland Human Research Ethics Committee, HREC/15/QRCH/159 and Ethics Committee of The University of Queensland 2016001491) and New Zealand (Health and Disability Ethics Committee HDEC 17/NTA/135).

Key Words:
Paediatric, Children, Respiratory Disease, Respiratory Support, Oxygen Therapy

ABBREVIATION	TERM
AHRF	Acute Hypoxic Respiratory Failure
BiPAP	Bi-level Positive Airway Pressure
CEWT	Children's Early Warning Tool
CPAP	Continuous Positive Airway Pressure
CRF	Clinical Research Form
ED	Emergency Department
EWT	Early Warning Tool
Fi02	Fraction of Inspired Oxygen
FPH	Fisher & Paykel Healthcare
FRC	Functional Residual Capacity
ICU	Intensive Care Unit
LCCH	Lady Cilento Children's Hospital
MDI	Metered Dose Inhaler
MET	Medical Emergency Team
NGT	Nasogastric Tube
NHF	Nasal High Flow
NIV	Non-Invasive Ventilation
PCCRG	Paediatric Critical Care Research Group
PEEP	Positive End Expiratory Pressure
PICU	Paediatric Intensive Care Unit
SpO_2	Transcutaneous Oxygen saturation
WHO	World Health Organisation

Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial

A Paediatric Acute Respiratory Intervention Study (PARIS 2)

ABSTRACT

Introduction: Acute hypoxemic respiratory failure (AHRF) in children is the most frequent reason for non-elective hospital admission. During the initial phase, AHRF is a clinical syndrome defined for the purpose of this study by an oxygen requirement and caused by pneumonia, lower respiratory tract infections, asthma or bronchiolitis. Up to 20% of these children with AHRF can rapidly deteriorate requiring non-invasive or invasive ventilation. Nasal high flow (NHF) therapy has been used by clinicians for oxygen therapy outside intensive care settings to prevent escalation of care. A recent randomised trial in infants with bronchiolitis has shown that NHF therapy reduces the need to escalate therapy. No similar data is available in the older children presenting with AHRF. In this study we aim to investigate in children aged 1-4 years presenting with AHRF if early NHF therapy compared to standard-oxygen therapy reduces hospital length of stay and if this is cost-effective compared to standard treatment.

Methods and Analysis: The study design is an open-labelled randomised multi-centre trial comparing early NHF and standard-oxygen therapy and will be stratified by sites and into obstructive and non-obstructive groups. Children aged 1-4 years (n=1512) presenting with AHRF to one of the participating emergency departments will be randomly allocated to NHF or standard-oxygen therapy once the eligibility criteria have been met (oxygen requirement with transcutaneous saturation <92%/90% (dependant on hospital standard threshold),

diagnosis of AHRF, admission to hospital and tachypnoea ≥35 breaths/min). Children in the standard-oxygen group can receive rescue NHF therapy if escalation is required. The primary outcome is hospital length of stay. Secondary outcomes will include length of oxygen therapy, proportion of intensive care admissions, health care resource utilisation and associated costs. Analyses will be conducted on an intention to treat basis.

Ethics and dissemination: Ethics approval has been obtained in Australia (HREC/15/QRCH/159) and New Zealand (HDEC 17/NTA/135). The trial commenced recruitment in December 2017. The study findings will be submitted for publication in a peer-reviewed journal and presented at relevant conferences. Authorship of all publications will be decided by mutual consensus of the research team.

Strengths and limitations of this study:

- This study is a pragmatic approach to test the efficacy of nasal high-flow therapy in children with acute hypoxemic respiratory failure.
- This study investigates if early use of nasal high-flow therapy compared to late or rescue nasal high-flow therapy is superior in regards to a patient centred primary outcome; the hospital length of stay.
- The study is performed in a wide variety of hospital settings including regional, metropolitan and tertiary hospitals; hence results will be highly generalisable.
- Blinding of the intervention is not possible, due to the visual differences between the two trial interventions.

INTRODUCTION

Of the 6.3 million children under the age of five years worldwide who died in 2013, over 1 million deaths were caused by acute respiratory infections causing acute hypoxemic respiratory failure (AHRF) (1). In limited-resource settings, children with severe pneumonia have a mortality rate between 13-20% and most deaths occurring with hypoxemia before therapeutic benefit of antimicrobials (2, 3). While the paediatric mortality due to respiratory infections has decreased in high-income countries, AHRF is the most frequent cause of hospital admission resulting in major consumption of healthcare resources (4-6). Asthma, pneumonia and bronchiolitis associated hospitalisations in children in the USA are estimated to account for over USD $3 billion of costs per year (4). There is an emerging trend to improve respiratory gas exchange with methods other than oxygen, particularly in the early stage of disease process aiming to prevent the progression of the disease (7). However, to date, the provision of positive pressure ventilation has been restricted to intensive care settings, which remains costly, is a limited resource and requires technical expertise. In view of the global burden of respiratory disease the World Health Organisation recognises oxygen as a potential life-saving treatment and is advocating to develop low cost and low technology oxygen delivery methods that can be delivered in most health care settings (8). Currently, standard oxygen therapy is delivered either using nasal prongs with low flow oxygen up to 4 L/min or using a face mask with oxygen flows of up to 8L/min. Nasal high flow (NHF) therapy is a new promising mode of respiratory support applied as an alternative to non-invasive ventilation, a potentially less tolerated respiratory support (4, 9). NHF therapy can be used very early in the disease process and requires little cooperation by the child. Several studies have shown that NHF therapy creates a distending pressure of the

lung with a PEEP effect of approximately 4-6 cmH_2O using flow rates of 1.5-2 L/kg/min in infants <12 months of age (10). NHF therapy also decreases the work of breathing (10-13). Because of its easy application and the fact that little cooperation of the patient is needed, NHF therapy in emergency departments (ED) has become increasingly popular (14-18). However, the data remains equivocal. A recent randomised controlled trial (RCT) using NHF therapy in adult patients with acute hypoxic respiratory failure (AHRF) showed that NHF therapy compared to standard-oxygen therapy or non-invasive ventilation resulted in reduced mortality in the ICU and at 90 days (19). Yet meta-analysis, including this study, failed to show any definitive benefit for treatment failure or in-hospital mortality (20).

The recent multi-centre PARIS RCT performed in Australia and New Zealand showed that NHF therapy in infants with bronchiolitis (aged < 12months) had a lower failure rate of 12% compared to standard-oxygen with 23% failure rate (21-22). In this study performed in EDs and paediatric wards in general hospitals or tertiary children's hospitals, no difference in the overall hospital length of stay or ICU admission rate was observed. These results are supported by an earlier single-centre RCT in patients with bronchiolitis which also found a lower failure rate with NHF, but no difference in hospital length of stay or length of oxygen treatment (23).

In a recent pilot study, we tested the feasibility of using NHF therapy in 552 children presenting with AHRF (excluded were infants with bronchiolitis <12 months of age). Included were children aged 0-16 years presenting with AHRF (SpO_2 <92%) to the ED and requiring hospital admission. The majority of children (79%) presenting with AHRF were aged between 1-4 years. Of these children allocated to early NHF therapy, 12% required

escalation of care compared to 17 % of children allocated to standard-oxygen therapy (data to be published). The data suggests that there is a beneficial role of NHF therapy in children with AHRF. Due to a lack of high-grade evidence we designed the PARIS 2 study, a randomised multi-centre RCT to test the hypothesis that children with AHRF on NHF therapy as a first line oxygen therapy have a reduced hospital length of stay compared with children on standard-oxygen therapy. We also aim to investigate whether this leads to a reduced requirement for escalation of care. A within trial health economics evaluation will be performed to determine the cost-effectiveness of the intervention, considering the heterogeneity of service users, health system, geographical and economic conditions and end implications for resource allocation from the payer's perspective. The modelling will account for the opportunity cost and affordability of the health system payer. In addition, a decision analytic model will be developed to account for longer term cost-effectiveness modelling.

Aim and Objectives

The PARIS 2 trial will investigate if the use NHF therapy in children presenting with AHRF will reduce the hospital length of stay. This will be achieved by comparing the use of early NHF therapy with standard-oxygen therapy.

The primary objective is to demonstrate if early use of NHF reduces the hospital length of stay.

The secondary objectives are to demonstrate if early use of NHF reduces the requirement to escalate therapy, reduces transfers to higher level of care such as intensive, reduces the

proportion of adverse events, to demonstrate ex post within-trial and ex ante longer term cost-effectiveness of high-flow therapy, to show reduced length of oxygen therapy and to ascertain comfort levels of children on high-flow.

METHODS

Study Design and Settings

The PARIS 2 trial is a multi-centre, randomised trial recruiting 1512 children aged 1-4 years requiring hospital admission for AHRF. The study will be performed in EDs (ED) and general paediatric wards of metropolitan hospitals and tertiary children's hospitals in Australia and New Zealand.

Definitions

AHRF is defined as children presenting to ED with increased work of breathing due to respiratory disease, having an ongoing oxygen requirement to maintain SpO_2 ≥90/92% (dependent on hospitals' current threshold for administering oxygen, which can either be 90% or 92%) with increased respiratory rate >35 breaths/min, and requiring hospital admission. The syndrome of AHRF represents an array of clinical diagnoses such as pneumonia, pneumonitis, acute lower respiratory tract infection, reactive airways (asthma) including small numbers with bronchiolitis older than 12 months of age. For the purpose of this study there will be two groups of patients investigated with a ***pragmatic and point of care definition,*** which includes clinically diagnosed: a.) *wheeze* (*obstructive) and reactive airway disease* with an oxygen requirement; and b.) *absent wheeze (non-obstructive) and parenchymal lung disease* with an oxygen requirement during hospital admission (Table 1).

Table 1: Clinical definitions for AHRF diagnostic groups

Diagnostic groups: *Obstructive Airway Disease*	**Symptoms**
○ Asthma ○ Reactive Airways Disease ○ Bronchiolitis for children >12 months	Oxygen requirement *AND/OR* ○ wheeze and/or cough ○ +/- viral illness ○ increased work of breathing and respiratory rate (>35/min) ○ +/- fever
Diagnostic groups: *Non-Obstructive Airway Disease*	**Symptoms**
○ Pneumonia – viral or bacterial ○ Aspiration ○ Acute lower respiratory tract infection ○ Bronchopneumonia ○ Acute respiratory distress syndrome ○ Pneumonitis	Oxygen requirement *AND* ○ cough ○ +/- viral illness ○ increased respiratory rate (>35/min) ○ +/- fever

Participants

Children will be identified and recruited by treating clinicians in the ED of the participating hospitals. All patients with AHRF (acute respiratory disease and oxygen requirement) in these locations will be screened for inclusion criteria in the study. Patients meeting all inclusion criteria and no exclusion criteria (Table 2) are eligible for randomisation.

Table 2: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Children aged 1 - 4 years plus 364 days presenting with AHRF • *and* require hospital admission despite initial assessment and therapy • *and* an ongoing oxygen requirement (SpO_2 <90/92%* in room air, dependent on hospital policy) • *and* have a persistent tachypnoea of ≥ 35 breath/min for ≥10mins at the time of randomisation	• Oxygen requirement and therapy in the emergency department existed for longer than 4 hours prior to inclusion (excludes oxygen given in ambulance or other hospital) • Previous use of high-flow during this illness episode • Upper airway obstruction • Craniofacial malformations • Critically ill infants requiring immediate higher level of respiratory support i.e. non-invasive or invasive ventilation, low level of consciousness *OR* • Critically ill with immediate need for intubation or non-invasive ventilation with the need of closer observation in ICU • Basal skull fracture • Trauma

	• Cyanotic Heart Disease (eg. Blue baby, expected normal saturation in room air <90/92%) • Home Oxygen therapy • Palliative Care • Cystic Fibrosis • Oncology • Child Protection patients

AHRF, acute hypoxemic respiratory failure; ICU, intensive care unit; SpO_2, oxygen saturation.

Consent Considerations

One of the primary challenges in performing research in an emergency setting is the inability to obtain true informed consent. Frequently, parents and guardians are not initially available when their child is brought into the ED. Furthermore, when parents or guardians are present, they are often too distressed by the situation to comprehend study procedures and there is not enough time to obtain informed consent (24-26). In all participating centres, prospective consent will be obtained from the parent or guardian where possible. When prospective consent is not possible or practical, and local legislation allows, patients will be randomised to the study and written informed consent to remain in the study will be sought from parents and guardians at the earliest possible time after emergency stabilisation of the child (consent-to-continue). Data for children whose parents and guardians do not wish for their child to remain in the study will be handled according to local hospital policies, and the data will not be available for analysis.

This study has ethical approval for consent-to-continue for participating Australian sites by the Children's Health Queensland Human Research Ethics Committee (HREC/15/QRCH/159) and Ethics Committee of The University of Queensland (2016001491). For sites in New Zealand approval has been received for prospective consent (Health and Disability Ethics Committee, 17/NTA/135) as the legislation of New Zealand does not allow delayed consent.

Ethics and dissemination

Ethics was first obtained with Children's Health Queensland Human Research Ethics Committee and Ethics Committee (CHQ HREC) and The University of Queensland in Queensland, Australia. All participating centres in Australia were subsequently approved ethically by CHQ HREC, totalling 11 centres, and three New Zealand centres by Health and Disability Ethics Committee.

The primary outcome results will be published in a peer-reviewed journal with secondary outcomes having separate manuscripts submitted for publication in peer-reviewed journals. On completion of the trial, following the primary outcome manuscript, results will be presented locally, nationally and internationally at conferences and respiratory workshops.

Recruitment, Randomisation and Blinding

Children 1-4 (4 years and 364 days) years of age with respiratory disease will be screened at the time of admission to hospital for presence of inclusion criteria. Identified patients will be treated initially as per the treating clinician for suspected underlying potential cause of AHRF which may include bronchodilator therapy for reactive airway disease, fluid bolus and other medications such as antibiotics. If AHRF (SpO_2 <90/92% in room air) symptoms persist and hospital admission is required, then the patient will become eligible and will be randomised to standard-oxygen or NHF therapy. Excluded are children as per Table 2. The

study protocol prescribes the oxygen delivery and weaning method only (standard-oxygen or NHF therapy). A web-based randomisation schedule with a block size of ten will be used with patients allocated 1:1 and stratified by site and by obstructive and reactive airway disease versus non-obstructive and parenchymal lung disease as defined by the admitting clinician.

Interventions and protocol

Treatment protocol for NHF therapy: NHF is set according to weight (Table 3) using the AIRVO-2™ system (Fisher & Paykel Healthcare (FPH) New Zealand). For children presenting with SpO_2 between 85 to 89/91% inclusive, the FiO_2 is initially set at 0.21 and SpO_2 observed for ten minutes. If SpO_2 remains <90/92% after ten minutes then FiO_2 is increased and titrated to achieve SpO_2 ≥90/92%. If SpO_2 has improved to ≥90/92% then NHF therapy is continued in room air. For children presenting with SpO_2 <85% the FiO_2 is immediately increased in 5% increments to achieve SpO_2 ≥90/92%. FiO_2 is adjusted for all children to achieve and maintain SpO_2 of 90/92-98% avoiding long periods of hyperoxia with SpO_2 of 100%. For any flow rates >25 L/min the high-flow rates are increased gradually over two minutes and the patient observed in terms of his/her ability to tolerate NHF therapy. Age and flow specific nasal cannulas will be used.

Table 3. Applied nasal high-flow rates

Weight	High Flow rates
0-12 kg	2L/kg/min

	Max 25 L/min
13-15 kg	30L/min
16-30 kg	35L/min
31-50 kg	40L/min
>50 kg	50L/min

Treatment protocol standard-oxygen: Standard subnasal 100% oxygen is offered at a rate of up to a maximum of 2 L/min (humidification according to standard hospital practice can occur) or via a face mask with a maximum of 8L/min and oxygen flow rates titrated to achieve SpO_2 of 90/92-98%.

The study design is only prescriptive for the oxygen delivery method. For the remaining respiratory management, the individual hospital internal protocols will be followed, including pharmacological management such as antibiotic or antiviral therapy. Infants and children who are admitted because of increased work of breathing or feeding difficulty but develop an oxygen requirement after admission to the paediatric ward are still eligible for the study.

Step-by-step guide to commence treatment arm – NHF therapy or standard-oxygen

- At the time of randomisation the clinician must be reassured that the patient has SpO_2 <90/92% in room air for preferably up to 10 mins of observational period
- *NHF intervention arm:* Appropriately sized high-flow nasal cannula will used with a gas mixture and flow according to the Table 3. Initially the gas mixture is set at a FiO_2 of 21% and increased if SpO_2 remains <90/92% after ten minutes of NHF therapy. If SpO_2 is <85% at enrolment then FiO_2 is immediately increased to achieve SpO_2 ≥90/92%. If the FiO_2 is greater than 40% (or up to 60% for no longer than 30 minutes and only used if needed from when NHF therapy first initiated) and increased work of breathing is present then a consultation with specialist paediatric center or local intensive care service must occur at this time. Increasing FiO_2 occurs in 5% increments at frequent intervals to maintain SpO_2 ≥90/02%. This can be 15 minutely to hourly according to local practice when performing observations, and depending on the patients requirements.
- The disposition of the study participant is dependent on local patient flow. No distinction in nursing ratio and care should be made between the two study arms.
- For the duration of bronchodilator administration, the NHF therapy is stopped and standard-oxygen therapy provided
- *Control intervention arm:* Standard-subnasal oxygen (humidification optional) or face mask oxygen will be offered according to local practice. Maximal flow rates as follows: subnasal oxygen up to a maximum of 2 L/min and face mask oxygen up to 8L/min. If SpO_2 remains <90/92% and/or the work of breathing is further increased since oxygen therapy commenced, then a consultation with a specialist paediatric centre or local intensive care service must occur at this time.

- Observations: Respiratory and heart rate and other clinical parameters hourly as a minimum (or according to hospital policy) and according to the Early Warning Tool (EWT) chart used in the participating study centre
- Weaning off NHF therapy: Only FiO_2 is reduced to maintain SpO_2 ≥90/92-98%. FiO_2 can be reduced to room air (21%). Once stable on room air NHF therapy can be stopped. At least one set of observations showing stable in room air must occur prior to the NHF therapy being stopped. If SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 minutes, and only increase FiO_2 when SpO_2 remains <90/92%. For the patient who starts and remains on room air only (21%) there are at least 2 hours of observations provided prior to stopping the NHF therapy. Again, if SpO_2 drops to <90/92%, restart NHF therapy with room air initially for 10 minutes, and only increase FiO_2 when SpO_2 remains <90/92%. Weaning of FiO_2 can occur 15 minutely to hourly according to local practice when performing observations, and depending on the patients requirements.

The study design is only prescriptive for the oxygen delivery method. For all other respiratory management, the individual hospital internal protocols will be followed, including pharmacological management.

Feeding whilst on NHF therapy. A nasogastric tube (NGT) is not mandatory in the use of NHF therapy but it is encouraged in the patients aged less than 2-3 years if clinically indicated. Insertion of a NGT remains at the discretion of the attending clinician. In patients who do not receive a NGT and are stable and wish to breast feed/drink and/or eat, the NHF therapy should be reduced to 2L/min (low flow therapy) via the same nasal cannula. This can be achieved by decreasing the flow to 2L/min and increasing the oxygen to 95% FiO_2 for a maximum of up to 20 minutes and then return the patient to the previous NHF therapy

settings. Patients who have had a NGT inserted should be assessed as to whether they can be fed. The use of the NGT over oral feeding whilst a nasogastric tube is *in situ* is preferred to prevent the risk of aspiration. Nasogastric feeding can be bolus or continuous at the discretion of the attending physician. Many of these patients will have an intravenous line *in situ*. Children who do not tolerate nasogastric feeds will have intravenous hydration.

Use of nebuliser and/or inhalation burst therapy for NHF therapy patients. For the duration of inhalation/burst therapy, the NHF therapy will be stopped and nasal prongs removed (leaving wiggle pads *in situ* if applied) and administer the burst/inhalation therapy administered. This will allow for greater face-mask seal with the metered dose inhaler (MDI) via spacer if used. For nebulisers there is no need for additional oxygen via nasal prongs. After the inhalation/burst therapy is complete NHF therapy will be returned with previous settings.

Escalation of care with or without change in therapy in both intervention arms (Figure 1). If at any time there is a change in oxygen therapy (standard-oxygen to NHF therapy or NHF therapy to standard-oxygen) data on reasoning for the change in therapy will be captured. Similarly, if there is an escalation of care to intensive care or high dependency unit the clinical criteria will be recorded to inform the decision-making process.

Study Outcomes and Definitions

Primary outcome is defined as the hospital length of stay (days) defined from admission to hospital (time of randomisation) to the time of discharge.

The secondary outcomes are:

1. Length of oxygen therapy since randomisation
2. Receiving a change in oxygen therapy in general ward settings from NHF to standard oxygen therapy (non-tolerance) or from standard oxygen to NHF therapy
3. Intensive care/high dependency care admission
4. Health care cost-effectiveness
5. Transfer to a tertiary hospital
6. Escalation of therapy such as non-invasive or invasive ventilation
7. Tolerance level of NHF therapy compared with standard-oxygen therapy
8. Clinical triggers that result in a change of therapy
9. Complications, serious adverse events (death before hospital discharge, cardiac arrest, pneumothorax or air leak syndrome

A pre-planned sub-analysis on the obstructive and non-obstructive groups to determine which, if any group responds differently to the two treatment arms and within the differing age groups (in one-year steps).

Additionally, a pre-planned sensitivity analysis will be performed using clinical criteria for the primary and secondary outcomes. They are as follows:

a.) heart rate remains >160/min for longer than 2 hours

b.) respiratory rate remains >45/min for longer than 2 hours

c.) oxygen requirement in NHF therapy arm exceeds FiO_2 > 40/50% (dependant on hospital standard policy) to maintain SpO_2 ≥90/92% or oxygen requirement in control oxygen arm exceeds standard oxygen therapy (2 L/min by nasal prong, or 8L/min by face mask) to maintain SpO_2 ≥90/92%

d.) the hospital internal Early Warning Tool (EWT) calls for medical review

Data Measures

Baseline demographics, age, weight, admission and discharge diagnosis, viral and bacterial testing, and medical therapy such as antibiotics/antiviral, steroids, inhaled or intravenous bronchodilators and other drugs will be captured during the entire stay in hospital. Physiological parameters (heart rate, respiratory rate, body temperature, oxygen saturation, work of breathing, comfort scale, oxygen requirement) will be obtained at the time of randomisation and after initiation of the allocated intervention, at any time of change of respiratory support and at time of escalation of care including admission of intensive care. Data on respiratory support provided in intensive care will be obtained. Data on feeding during the study will be also captured.

Clinical Tolerance for NHF therapy treatment arm**.** It is recognised that NHF therapy is a relatively new therapy for children with mild to moderate severity of respiratory illnesses. The tolerance level of placing nasal cannula with high flows in younger children, particularly the 1-4 year age group, is unknown. This RCT aims to additionally investigate the tolerance level of NHF therapy. A 100mm unmarked visual analogue scale (VAS) will be used as a measurement instrument. Both the parent and the nurse caring for the patient will separately assess the intensity of respiratory patient-comfort level twice during admission: firstly, at one-hour post commencement of oxygen therapy and secondly between 4-48 hours post commencement of oxygen therapy and document the comfort score that they believe the child is experiencing at that point in time. One end of the scale is marked with “no discomfort” and the other end marked as “maximal imaginable discomfort”. The VAS will measure both standard-oxygen therapy and NHF therapy treatment arms for level of comfort.

Data Management

Study data will be obtained either directly from hospital records, electronic medical records or copies and entered after verification into the clinical research form (CRF). The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All CRF and study documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The document/forms will be stored and locked away as per site specific requirements and regulations for each individual hospital. Ongoing surveillance and adherence to the study protocol will be monitored by the Coordinating Principal Investigator and the steering committee, who are meeting via teleconference at 3-monthly interval. All serious adverse events, protocol deviations and protocol violations will be submitted to the chief investigator and all serious adverse events and protocol violations will be submitted to the approving HREC and local RGOs. All local regulatory process will be followed to ensure adherence to local governance requirements. An independent Data and Safety Monitoring Board (DSMB) that has been used in the past for other respiratory trials will be used. The DSMB will consist of an experienced DSMC Chair, clinical expert, statistician and a secretariat. An interim analysis will be undertaken by the DSMB after 100 participants have been enrolled into the study but only analysed for safety aspects. This had already occurred at the time of the publication of this protocol and the DSMB recommended to continue the trial.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN (SAP)

Sample size. The sample size calculation is based on a two-sided, randomised, parallel group trial design with total length of hospital stay as the primary outcome and survival analysis as

the primary method of analysis. We consider a difference in length of hospital stay of at least half a day as clinically meaningful, however for the sample size calculation this will be reduced to 0.4 day to increase the sample size to adjust for the effect of clustering. Assuming a median length of hospital stay in the control therapy arm of two days (based on pilot data), compared with a median length of hospital stay in the NHF arm of 1.6 days, 5% level of significance and 90% power we require 1209 children. To allow for up to 20% non-compliance we require 1512 children in total; 756 in each treatment group. We estimate a 50-80% enrolment rate of eligible patients.

Statistical analysis plan. Descriptive statistics will be used to report on the baseline characteristics of the total study cohort stratified by treatment group. Kaplan-Meier plots will be used to graphically describe and compare the primary outcome (length of hospital stay) as well as duration of oxygen therapy. Analyses of secondary binary outcomes will be based on chi-squared test for proportions and the absolute difference between treatment groups will be reported as the risk difference with a 95% confidence interval. An independent samples t-test will be used for normally distributed continuous measures; Mann-Whitney U test for non-normally distributed continuous outcomes. Exploratory analyses will be conducted on the subset of patients who require escalation of treatment. These are conditional analyses that are not based on comparing complete randomised groups hence caution will be used needed when interpreting the results. We plan to compare length of ICU stay between treatment groups for the subgroup of patients that are admitted to ICU. All analyses will be by intention-to-treat. Statistical significance is set at the 0.05 level.

Health economics evaluation. We will build an ex-ante longer term decision analytical model and also undertake ex-post within-trial modelling, to determine the cost-effectiveness of

treatment compared to usual care. An appropriate bepoke health economics data collection tool will be developed to provide critical data for these models. Unit costs will be extracted from standard sources. To provide longer-term analysis, we will build a bespoke Decision Analytical Model to estimate cost-effectiveness under the horizon of 5 years. The model will be based on both aggregate resource, cost use and health state transitions data from literature, expert opinion, along with our newly collected data in the RCT. Models will include sensitivity analysis, and outputs will include Cost Effectiveness Acceptability Curves (CEAC) – these will display the probability of cost-effectiveness at varying thresholds of net monetary benefit (NMB). Following a Markov Chain modelling approach, we will use Monte Carlo simulation methods to incorporate the occurrence and timing of events. The main issue with such ex-ante evaluation is uncertainty, and we will use standard bootstrap methods to account for this in our estimates. This will provide us with a sensitivity analysis of differences in potential costs depending on demographics and socio-economic status. The model will be constructed and continuously updated with new data as it becomes available throughout the project. A standard within-trial cost utility analysis will be undertaken under the horizon of 5 days. This will compare costs and benefits in terms of resource use and quality adjusted life years (QALY) gained. Resource use and travel data will be collected with the bespoke tool and the collated unit costs will be assigned to the resource utilization to provide overall costs for both arms of the trial. Benefits will be assessed using appropriate quality of life instruments, e.g. EQ5D-5L and PEDSql. The analysis will be from the health care provider perspective but with an additional societal perspective, to include for example, consumer travel costs. Probability sensitivity analysis will be provided to give the probability of cost-effectiveness at each threshold level of net monetary benefit. The data from this trial will then feed into our Decision model, enhancing the model further with current and comparable data.

Outcomes and Significance

Providing the hypothesis of the study can be proven, the following impact on future health care is expected: i.) Reduction in hospital length of stay for patients aged 1 to 4 years with AHRF, ii.) Reduction of transfers of patients aged 1 to 4 years with AHRF to specialist paediatric centres - 'keeps patients in their regional hospitals' and potentially gives the regional centres more autonomy in managing their patients with best respiratory practice, iii.) That early intervention reduces the number of patients requiring escalation of treatment, iv.) Reduction in health care costs and demonstration of cost-effectiveness of NHF therapy, v.) Potential to expand NHF therapy to older children with AHRF, vi.) Greater expansion of knowledge for nursing and medical staff on the use of NHF therapy and the benefits and non-benefits in this population of children, vii.) Informing the use of HNF therapy in less developed countries in this population of children and viii.) Development of strategies to implement NHF therapy safely in the described study population.

Limitations

The intervention of high-flow therapy cannot be blinded and a certain clinician driven bias may occur. The escalation of care is driven by clinical criteria and judgment and there is the potential bias to favour one intervention over the other. However, our previous high-flow trial in bronchiolitis showed that this element was not cofounding the study outcomes (22).

Data Sharing.

Data generated by this study will be shared and available in deidentified form upon reasonable request, wherever legally and ethically possible.

Patient and Public Involvement

For the study protocol there was no direct patient or public involvement.

Current status of the trial

The study enrolment has commenced across 14 centres, with 1105 children recruited by August 2019. The expected end date of recruitment to this trial is December 2020.

Sites involved in the study include:

Australia

Queensland

Queensland Children's Hospital

Gold Coast University Hospital

Caboolture Hospital

Ipswich Hospital

Redcliffe Hospital

Townsville Hospital

The Prince Charles Hospital

New South Wales

John Hunter Children's Hospital

Victoria

Royal Children's Hospital Melbourne

Monash Children's Hospital

Western Australia

Perth Children's Hospital

New Zealand

Starship Children's Health

KidzFirst, Middlemore Hospital

Waikato Hospital

DISCUSSION

This large multi-centre randomised trial will provide the much-needed high grade evidence of the efficacy of NHF therapy compared to standard-oxygen in the ARHF children aged 1-<5years. This study will also provide a unique opportunity to investigate the safety profile off high-flow in children with acute hypoxemic respiratory failure. We will capture data on health resource use and quality of life and the results can be utilized to inform best practice in use of high-flow outside intensive care settings.

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LEGENDS

Figure 1.

Study flow diagram. AHRF, acute hypoxemic respiratory failure; NHF, nasal high-flow; ICU, intensive care unit; RR, respiratory rate; SpO_2, oxygen saturation; ED, emergency department.

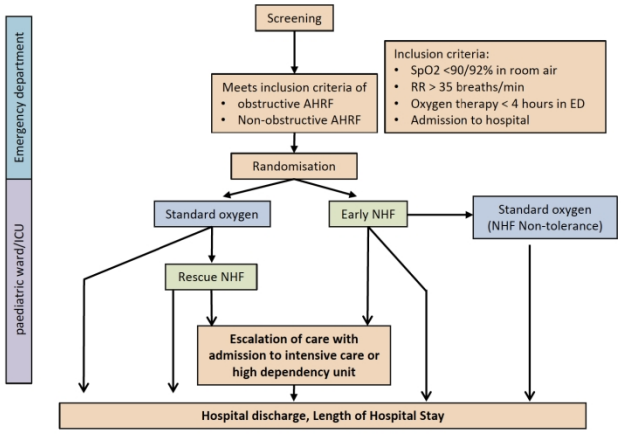

Figure 1. Study flow diagram. AHRF, acute hypoxemic respiratory failure; NHF, nasal high-flow; ICU, intensive care unit; RR, respiratory rate; SpO_2, oxygen saturation; ED, emergency department.

Figure 1. Study flow diagram. AHRF, acute hypoxemic respiratory failure; NHF, nasal high-flow; ICU, intensive care unit; RR, respiratory rate; SpO2, oxygen saturation; ED, emergency department.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (PAGE 1, 7-8)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry PAGE 4
	2b	All items from the World Health Organization Trial Registration Data Set N/A
Protocol version	3	Date and version identifier VERSION 13.0 DATED 7TH DEC 2019
Funding	4	Sources and types of financial, material, and other support PAGE 5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors PAGE 5
	5b	Name and contact information for the trial sponsor PAGE 5 - NHMRC
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) PAGE 5
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (PAGE 7, 9-11)
	6b	Explanation for choice of comparators (PAGE 11, 16-18)
Objectives	7	Specific objectives or hypotheses (PAGE 11-12)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (PAGE 12-20)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained. PAGE 12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) PAGE 14
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (PAGE 16-19)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) PAGE 22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (PAGE 21-22)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (PAGE 27-28)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (PAGE 24-25)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size N/A
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions PAGE 16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned PAGE 16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions PAGE 16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how NOT DISCUSSED
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (PAGE 23-24)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols NOT DISCUSSED – USE INTERNAL PROCESSES
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (PAGE 23-24)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (PAGE 23-24)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (PAGE 23-24)

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (PAGE 23-24)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (PAGE 5 AND 24)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial PAGE 24
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct PAGE 24
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor NOT DISCUSSED – USE INTERNAL PROCESSES
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval PAGE 5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) NOT DISCUSSED – USE INTERNAL PROCESSES
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (PAGE 15-16)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial PAGE 25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site PAGE 4-5
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (PAGE 15, 23-24)

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation NOT APPLICABLE
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions NOT DISCUSSED
	31b	Authorship eligibility guidelines and any intended use of professional writers. NOT DISCUSSED – USE INTERNAL PROCESSES
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - NOT DISCUSSED – WILL PROVIDE WITH MAIN OUTCOME PUBLICATION
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates NOT PROVIDED
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable NOT DISCUSSED AS NOT REQUIRED.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.